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ORIGINAL ARTICLES

THE ETIOLOGY OF ACUTE INFLAMMATIONS OF THE NOSE, PHARYNX AND TONSILS*

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I. INTRODUCTORY

THAT a state of confusion exists as to the etiology of the acute inflammations of the upper respiratory tract is evident upon casual excursion into the literature. A more patient search, however, reveals certain material, notably in the form of recent laboratory work, from which definite conclusions can be drawn, and in whose light the discussions of the "common cold" in the current texts is clearly seen to be obsolete. The present paper is concerned with the etiology of the acute inflammations of the nose, pharynx, and fauces, particularly with reference to recent laboratory inquiries. The question of the excitation of sporadic infections by exposure of the body surface to cold is dwelt upon in considerable detail—much more at length than its relative importance deserves, indeed—simply because the newer data here presented is the contribution of the present authors.

Since the early days of bacteriology, attempt has been made by the several proponents and opponents of the infectious theory to refer the "common cold" on the one hand to the action of a specific microorganism, and on the other to

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The original experiments described in this paper were chiefly performed at Washington University, St. Louis, by the above authors. The paper itself is a revision of a dissertation submitted by Stuart Mudd and awarded for 1920 the Boylston Medical Prize of Harvard University, which is open to public competition. By an order adopted in 1826, the Secretary of the Boylston Medical Committee was directed to publish annually the following votes:

1. That the Board does not consider itself as approving the doctrines in any of the dissertations to which premiums may be adjudged.
2. That, in case of publication of a successful dissertation, the author be considered as bound to print the above vote in connection therewith.

various environmental and constitutional causes, such as exposure to changes of temperature, the "lithemic diathesis," and what not. Although perhaps laudable as philosophic ideals, such efforts to explain the many phenomena involved by a single cause are less deserving scientifically, and have met with just failure. The "common cold" is, as a matter of fact, in most instances the result of a local infection, but there are many types of "cold" and many infectious agents responsible for them; and the effect of various constitutional and environmental factors in determining infection is often of great importance. Furthermore there are many acute inflammations of the upper respiratory tract not primarily due to the local action of microorganisms, but rather the local expression of chemical or mechanical irritation, of thermal trauma, of nervous reflexes, of drug intoxications, of constitutional disease, or of anaphylaxis.

II. BACTERIOLOGY OF THE COMMON COLD

The studies of a number of investigators have shown that, although the entrance of the nose is swarming with bacteria, the flora of the nasal cavities proper in health is kept exceedingly sparse by the action of the ciliated epithelium, the trickling of the lacrimal and mucous secretions, the inhibitory action of the mucus, and by phagocytosis. (Thomson, 1913, p. 7.) The folds of the pharyngeal mucosa and especially the crypts of the tonsils are, on the other hand, known to maintain even in health an abundant flora, including often potentially pathogenic organisms (e.g., see Davis, 1920). Bacteriologic studies of the nose and throat in the course of acute "colds" have usually shown the presence of microorganisms in unwontedly large numbers, often with one form so predominating as to suggest for it an etiologic relationship with the cold. In a number of instances immunologic and inoculation data have supported the bacteriologic evidence and would seem to warrant assumption of a causal relationship between the bacteria and the colds in question.

In 1873 Hüter described a micrococcus as a cause of coryza (cited by Benham, 1906).

Hajek (1888) described a large diplococcus, the *Diplococcus coryzæ,* in the early stages of acute colds. He advances no other evidence in support of his bacteriologic findings, however. Certainly in the light of recent experience with influenza, the mere presence of bacteria in large numbers during an inflammation cannot be regarded as valid ground for considering them its cause. (For a discussion of bacteriologic methods in estimating the relationship of microorganisms to respiratory disease, see Allen, 1913.)

Paulsen (1890), examining twenty-four cases of cold of diverse clinical types, some with history of exposure to other persons with colds, and others following exposure to chilling, found various cocci and bacilli as the predominating organisms.

Cautley (1894-95) found an aerobic diphtheroid bacillus, oval, with a tendency to polar segregation of the protoplasm, in seven of eight cases of acute cold of various types. The infection started in trachea, pharynx or nose. Cautley, believing the organism responsible for coryza, called it *B. coryzæ segmentosus.* Gordon (quoted by Benham, 1906) found Cautley's bacillus in all of seven cases of cold. Gordon injected two guinea pigs with the organism

and noticed they were sick a few days, but recovered. R. Prosser White (quoted by Benham, 1906) found Cautley's bacillus in seventeen of twenty-one cases. Inoculation experiments upon the noses and genital tracts of guinea pigs, rabbits and monkeys were negative.

Benham (1906) found a diphtheroid organism he regards as identical with Cautley's bacillus in twenty of twenty-one cases of cold. Micrococcus catarrhalis was also present in many cases. He concludes "in view of the fact that nasal discharge was not a prominent feature of my series of cases, it seems likely that the diphtheroid organisms are rather a cause of a painful sore throat with headache, malaise and muscular pains, irritable cough and scanty viscid expectoration. Whether they cause coryza—a cold in the head—is at least open to question, especially in view of the presence of M. catarrhalis in nearly half my cases." Benham therefore gives Cautley's B. coryzæ segmentosus the less committal name of *Bacillus septus.*

Micrococcus catarrhalis was found by R. Pfeiffer (quoted by Neisser in Kolle and Wassermann's "Pathogenen Mikroörganismen," 1913) in enormous numbers in the sputum of an epidemic of mildly febrile cases of bronchitis. Gohn and H. Pfeiffer (1902) found this diplococcus in eighty-one of one hundred forty cases of respiratory tract infection. They regarded it as a saprophyte which can under appropriate circumstances give rise to acute or subacute infection. Bezançon and de Jong (1905) found this organism very frequently in an influenza-like epidemic in Paris. Along with M. catarrhalis they found Micrococcus paratetragenus, pneumococcus, Friedländer's bacillus, staphylococcus, streptococcus and diphtheroids. Dunn and Gordon (1905) believed the Micrococcus catarrhalis to be the chief organism in a severe epidemic in Hertfordshire with clinical manifestations in different cases simulating cerebrospinal fever, influenza and scarlatina. Allen (1906) made claim to have isolated M. catarrhalis with ease from each case examined in a severe local epidemic of colds in England.

Neumann, (1902) as a result of a considerably more extensive and thorough bacteriologic study than the foregoing, concluded that virulent *diphtheria bacilli* and the *pneumococcus* at least, perhaps other organisms, could produce the ordinary cold.

He summarises as follows the results of his study of the flora of the noses of 111 normal persons and of 95 suffering from nasal affections of various sorts:

"The total number of bacterial species found was 19. Nevertheless in most cases there are relatively few different species found present together. Most frequently are found diphtheroid bacilli and white micrococci. Less frequently orange, gray and yellow micrococci, pneumococci, streptococci, Friedländer's bacilli, diphtheria bacilli, isolated colon bacilli, yeast, molds, mixed bacilli, sarcinæ and still a few other organisms.

"Micrococcus pyogenes albus is present in 86 to 90 per cent, diphtheroids in 98 per cent of the cases, so that one can justly assert that the latter occur in every sound and pathological nose. The more delicate form (B. xerosis) is much more frequent than the more luxuriantly growing form (Hoffman's bacillus.)

"In colds the pathogenic organisms, pneumococcus, Friedländer's bacillus, streptococcus pyogenes and diphtheria bacillus are more prominent than in normal noses.

"The diphtheroid bacillus is not virulent. Seventy-eight strains cultivated from different noses in no case killed guinea pigs. In a few cases only weak infiltrations appeared at

the site of injection. The organism cannot be brought into relationship with the origination of the cold and is only to be considered as a harmless saprophyte.

"Certainly it is demonstrated that virulent diphtheroid bacilli and Fränkel's pneumococcus can cause the clinical picture of the common cold. Whether and in what way other pathogenic germs are concerned in it, is still to be answered.

"A specific cause of the cold has not been found in the investigations."

Claims for the *Bacillus of Friedländer* as a cause of "cold" are advanced, with immunologic support, by Allen (1906). Allen asserts that in each of two epidemics of a severely infective character in every case examined within the first 24 hours, and in some later, the bacillus was found. "It was of a very virulent stamp, being pathogenic not only for mice and guinea pigs but even for rabbits; it also clotted milk and fermented broth with ease."

Claims for an etiologic relationship are based upon the following statements, which, if true, would seem to establish the point:

"The appearance of the bacilli in the nasal passages of the people affected synchronized with the onset of the attack.

"The organism and colds disappeared together.

"The opsonic index of the patient's blood, which was particularly studied to the bacillus of Friedländer was affected by a cold precisely in the way that would be expected in the case of an infection by that organism, that is it rose steadily to a maximum, remained there for some time, then steadily fell to about unity during a period of perfect freedom from cold. Second and third attacks had precisely similar results.

"The appearance in the house of a person whose nasal passages were known to be infected by the bacillus of Friedländer sufficed to start an epidemic of colds on several occasions; and from the noses of such as were examined, the bacillus of Friedländer was also isolated."

Work somewhat more convincing than any of the foregoing has been reported by Tunnicliff (1913, 1915) and Howell (1915). The organism is an anaerobic curved bacillus. *B. rhinitis, Tunnicliff.*

Miss Tunnicliff, working in Chicago, found her bacillus present in 6 per cent of some 86 normal noses examined, in 98 per cent of 82 cases of acute coryza, and in 90 per cent of twenty odd cases of chronic rhinitis with mucoid discharge.

A slight rhinitis was produced three times in human subjects by swabbing a nose free from B. rhinitis with a pure culture. The infection began from 6 to 8 hours after the inoculation and lasted about 48 hours. The organisms were present in fairly large numbers in the nose and pharynx (in the cases with pharyngitis) 18 hours after the inoculation, and persisted for three days in two of the cases. Cultures were made twice, and the organisms isolated in pure culture both times. The opsonic index was taken during two of the infections. Both times it fell below normal, rising high above normal as the infection disappeared.

Vaccination of two patients with B. rhinitis produced a primary depression of the opsonic index followed by a rise above normal.

Miss Howell found that, using B. rhinitis as antigen, fixation of complement is obtained with the sera of persons with acute rhinitis and of persons injected with the bacillus after it is killed by heat. The fixation is most marked a few days after the onset of the infection and lasts only a short time. Sera

of normal persons and of patients with various infectious diseases do not give complement fixation with the Bacillus rhinitis.

It is difficult to escape the conclusion that B. rhinitis was causally related to these cases of acute coryza about Chicago.

That *streptococci* may be responsible for infections of the nose, and more especially the pharynx and tonsils, has been shown by many authors (vide Lingelsheim 1912, and Barnes, 1914, p. 67).

Mathers (1917) made a careful bacteriologic study, using aerobic, anaerobic and filtration methods, of an epidemic of acute respiratory infection in Chicago, which resembled the influenza of 1889-92. He concluded that a virulent hemolytic streptococcus was the probable cause.

Floyd (1920), as a result of bacteriologic study and vaccine therapy of the winter colds occurring in and around Boston, concluded that in acute rhinitis the organism commonly found belongs to the staphylococcus group, and that somewhat less frequently the hemolytic streptococcus has appeared. In acute pharyngitis "almost invariably the initial infection is produced by the member of the streptococcus group."

Pneumococcus has also frequently been recognized as concerned with infections of the upper respiratory tract. (v. Abel, 1892, Neufeld u. Händel, 1912; Floyd, 1920.)

Discussion of *B. influenzæ* has purposely been left out of this paper. Under this caption, however, may be quoted the conclusions of R. W. Allen (1913) based upon some ten years of bacteriologic study of the respiratory diseases, in England.

"To summarize," he writes, "it would appear that any of the seven organisms, B. influenzæ, pneumococcus, streptococcus, M. catarrhalis, M. paratetragenus, B. septus, and bacillus of Friedländer, alone or in varying combinations, may be responsible for a catarrhal condition of the upper respiratory passages. In perhaps 40 per cent of cases one organism so predominates as to justify the conclusion that it is *the* cause of the attack; more often two or more organisms are associated together, the B. influenzæ with the pneumococcus or M. paratetragenus, the B. septus with the M. catarrhalis or M. paratetragenus, so that it becomes very difficult to decide which organisms stand in a directly causal relationship to the attack. My own belief is that mixed infections from the beginning are fairly common.

"In uncomplicated purulent nasal catarrh the streptococcus is the most frequent cause, next to it the Staphylococcus aureus. When sinus complications coexist, the B. influenzæ and pneumococcus are by far the most frequent bacteria concerned."

Blake and Cecil (1920) have also recently reported successful infection of monkeys with B. influenzæ introduced both into the nose and intratracheally.

Although any attempt at adequate discussion of the etiology of epidemic influenza is outside the scope of the present paper, its virus must be included among those capable of giving rise to acute inflammation of the upper respiratory tract. We would express our own opinion, too, that the attributes of a specific, labile, and elusive virus, to which so many converging lines of evidence have pointed, are extraordinarily well filled by the *filterable virus* which has been the object of the past two years of careful study by Olitsky and Gates at the Rockefeller Institute (Olitsky and Gates, 1920). The results of these studies will be further presented by these authors in the February

and March, 1921, numbers of the Journal of Experimental Medicine. For a bibliography and brief review of "The Epidemiology and Etiology of Influenza" reference is made to A. J. McLaughlin (1920).

A *filterable virus* seems without question to be the causative agent in the coryza of one fairly well defined type. Kruse (1914) diluted the secretion from the nose of an assistant with coryza, passed it through a small Berkefeld filter, and dropped a few drops of the filtrate on the nasal mucosa of each of twelve men. Four of them developed colds in from one to four days. In a second experiment 42 per cent of thirty-six subjects so inoculated developed coryza within from one to four days. Kruse could find no living organisms in his filtrates by bacteriologic methods.

Foster (1916) in repeating and extending this work, passed through a small Berkefeld N filter, with aseptic precautions, the nasal secretion of persons suffering from acute colds. This filtrate he proved to be free from ordinary bacteria both by aerobic and anaerobic methods. From three to six drops of the filtrate were placed in each nostril of each of ten soldiers. Nine of the ten men developed the usual symptoms of acute coryza in from eight to thirty hours. Inoculated into tubes of tissue broth or tissue ascitic fluid under petrolatum, after the method of Noguchi and Flexner with rabies and poliomyelitis virus, this filtrate produced a growth which could be subcultured apparently indefinitely. Specimens of these subcultures were again diluted, passed through a Berkefeld filter, and a few drops allowed to run into the noses of eleven healthy soldiers, every one of whom developed, after an incubation period of eight to forty-eight hours, acute colds. Cultures from these individuals' nasal secretions gave the same appearance as the original cultures. They contained an abundant growth of a pleomorphic virus varying from minute globoid bodies to coccoid forms larger than staphylococci, the latter apparently in some instances with small globoid buds. (Foster 1917.)

The clinical picture described by Foster both for his original patients and for the subjects of the inoculation experiments is worth giving by a typical case. The patient "complained of lassitude, chilly sensations, sneezing, unilateral nasal stuffiness, dull frontal headache with a feeling of oppression over the eyes, impairment of smell and moderate aching pain in the extremities. There was the usual lacrimation, a copious, thin, mucoid nasal discharge which excoriated the upper lip and the alæ of the nose, and a very red, moist, swollen and boggy mucosa. The temperature was normal."

The contention of Professor M. J. Rosenau, in whose laboratory Foster's work was done, that this type of acute coryza deserves to be considered a clinical entity, would appear to be well founded. It is extremely interesting that a symptom-complex has been separated on purely clinical grounds from the remaining congeries of nose and throat affections. Coolidge (1918, p. 92) writes: "But there is one form of 'symptom-complex' so common and constant that it might well be classed as a distinct and definite disease, and it is to this disease that the word 'cold' is most frequently applied." His description of it closely corresponds to Foster's.

A survey of the literature then would seem to warrant the following conclusions:

1. A common and fairly well defined clinical entity, an acute coryza, exists, probably with the filterable virus of Kruse and Foster as its causative agent. This affection is readily communicable and probably does not depend to any great extent upon the action of exciting factors in depressing the resistance of the subject. 2. A heterogenous group of pure and mixed infections of the nose, pharynx and tonsils exists with various clinical pictures—some closely approaching that of Foster, others mere circumscribed inflammations—and with any one of a considerable number of bacteria capable, under appropriate circumstances, of acting as causative agents.

The microorganisms whose etiologic rôles seem to the writer to be best established are pneumococcus, streptococcus, B. diphtheriæ, B. rhinitis, Friedländer's bacillus, and B. influenzæ. Strong bacteriologic evidence, unsupported, however, so far as the writer knows, by immunologic or experimental data, has been advanced for M. catarrhalis, B. septus, M. paratetragenus, and S. aureus. The possibility that still other organisms may be primarily or secondarily involved is, of course, not excluded. Wide variations in virulence exist, both between different organisms and probably from time to time in the same bacterial strain (see Allen, 1913); some organisms are doubtless capable of causing infections in epidemic proportions, nearly or quite independent of accessory exciting factors; others may exist as harmless saprophytes upon the mucous membranes, causing infection only when the resistance of their host, local or general, is lowered by some exciting factor.

III. EXCESSIVE CHILLING AS AN EXCITANT OF INFECTION

It is not the purpose of the present dissertation to attempt a sifting of the large amount of evidence, collected chiefly by ordinary and by clinical observation, which bears upon the question of the predisposing and exciting factors of upper respiratory infections. Suffice it to say that anything which lowers resistance, general or local, may disturb the equilibrium between host and parasite in the direction of exciting infection. The present section of this dissertation will concern itself with one particular factor only, namely, exposure to cold.

In the consideration of cold as an excitant of mucous membrane infection the issue has been somewhat confused by certain other effects of chilling. One of the immediate results of exposure, for instance, may be a transient rhinorrhea having no necessary relation to "catching cold." Again a very slight draft of cool air may, in the stage of onset of a cold, be accompanied by a feeling of chilliness or even a rigor—this is obviously an effect and not, as it is sometimes wrongly considered, an antecedent of the infection.

But, in addition, it would seem to be a fact attested by long and general experience that excessive exposure to cold may be an actual excitant of rhinitis, pharyngitis or tonsillitis. Certainly the weight of authority is in support of this thesis. Of the laryngologic texts, the following recognize chilling as an efficient factor in exciting infection: Grayson (1902), Ballenger (1908), Coakley (1914), Kyle (1914), Wright and Smith (1914), Phillips (1919), and Tilley (1919). However, Thomson (1913) and Coolidge (1918) are skeptical. In sup-

port of the affirmative are Marchand, in Krehl u. Marchand's Handbuch d. Allgemeinen Pathologie, (1908), Lingelsheim in Kolle u. Wassermann's Handbuch d. Pathogenen Mikroörganismen (1912), Packard in Osler and McRae's Modern Medicine (1914), Barnes, "The Tonsils" (1914), Barker, Monographic Medicine (1916), MacCallum's Pathology (1920), and Rosenau (1920). The experiments of Miller and Noble (1916), who have shown that the liability of rabbits to respiratory infection by B. bovisepticus is heightened by exposure to cold after overheating or by overheating after chilling are extremely suggestive in this connection. We, too, have obtained some experimental evidence (Mudd and Grant, 1919, Grant, Mudd and Goldman, 1920) as will be shown later, which would seem to afford support to the thesis that mucous membrane infection may be excited by chilling the body surface.

What would seem to be conclusive evidence in establishing excessive exposure to cold as an efficient excitant of acute upper respiratory affections has recently come from Germany in the form of statistics for large bodies of troops during and before the war. (Schade, 1919.) The data in brief is as follows:

(a) Comparison of the incidence of disease during the mild winter of 1915-1916 and during the very severe winter of 1916-1917. The increase of disease incidence rose to almost twice the total in 1916-1917; the largest single factor in this increase was the heightened incidence of respiratory affections, which in February, 1917, rose to 7.6 times the usual summer rate.

(b) Comparison of sickness among 8,000 infantry troops of whom one part (2700 men) were subjected for three days and nights to conditions of severe cold and wet, while the rest stayed behind during the same weather in village quarters. In spite of hardening by the three previous years of trench warfare, the incidence of acute respiratory diseases, "rheumatic diseases" and acute urinary affections, chiefly acute bladder irritation with diurnal and nocturnal enuresis, was four times as great among the exposed as among the sheltered troops.

(c) Comparison of sickness among 8,000 infantrymen of whom one part (4500 men) were exposed three days and nights to extreme cold (–9° to –12° C. midday temperature) accompanied by a sharp, gusty wind, while the remaining 3500 men were in sheltered quarters. The exposed troops comprised 160 cases of "exposure disease"—i. e., 128 acute respiratory cases, 28 of rheumatism, 4 of severe bladder irritation, and 4 of freezing. Reckoned on a basis of equal numbers of men, the sheltered troops had only 40 cases of "exposure disease" and one of freezing.

(d) Comparison of daily incidence during three months of diseases of the respiratory tract with that of "rheumatic" affections among 8,000 troops. The curves are clearly parallel. On the same days in which the number of cases of respiratory tract catarrh increased, the cases of rheumatic pain became more numerous also.

(e) Comparison of incidence of "diseases of exposure" (see above) with that of cases of freezing. Daily curves for 8000 troops show parallelism.

The sanitary reports of the Prussian war ministry, comprising all detected cases of diseases among all the men of Prussia, Saxony and Württemberg in com-

pulsory military service (more than a half million annually) have been analyzed and plotted for monthly intervals over twelve years. Of upper respiratory diseases, excluding tonsillitis, 428,714 cases are included, of "acute muscular rheumatism" 72,179 cases, and of "frost-bite" 12,898 cases. Always the upper respiratory diseases show in January and February their steep winter rise; year by year the incidence of "muscular rheumatism" and of frost-bite follow in astonishing parallelism.

The curves of incidence by month for the whole twelve years combined are also given. The curve for frost-bite rises from the base line in October steadily to a crest in February and returns to the base line in May. It is nearly symmetrical and of the form of the familiar frequency polygon. The curve for tonsillitis (271,852 cases) rises closely parallel to the frost-bite curve from December to its peak, almost identically placed in February, and descends again almost parallel until April. The tonsillitis curve is distinguished, however, by a small secondary peak in November and by its slope becoming less steep during the spring and summer so that the base line is not approached before the October rise begins. The curve for upper respiratory diseases exclusive of tonsillitis runs nearly parallel to that of tonsillitis, including the secondary mode in November, but reaches its summit in January.

It is difficult to see how one could study the curves and yet escape the conclusion of the author that "chilling by the weather and the occurrence of respiratory tract catarrh stand certainly in the closest correlation."

Such close parallelism, as Schade also gives curves to show, is not to be found between the incidence of diseases of exposure and air temperature; it is apparently with the cooling power of the air, as determined by temperature, humidity and by movement, and expressed in the frequency of frost-bites, that the parallelism exists.

Incidentally, to digress for a moment, the efficacy of the common respiratory affections in lowering resistance and preparing the way for the specific infections of mumps, scarlet fever, and measles is shown in other curves in this most illuminating paper.

It is probable that in the general population, where the physical condition does not average so high as among the young men studied by Schade, and where exposure is not so severe, the element of contagion would play a much larger and weather a much smaller part in determining incidence of respiratory affections. However, even here, excluding the great epidemics, influenza and pneumonia begin with the frost, become severe when the temperature averages below freezing, reach a maximum when the temperature is lowest and then decline. (Jour. Am. Med. Assn., editorial, 1920, lxxv, 1500.)

As to the mechanism of excitation of infection by chilling the skin, current opinion has gone curiously astray. Since the classic studies of Pasteur with anthrax and fowls with wet feet many authors have shown that animals whose blood temperatures have been lowered may show decreased resistance to bacterial infection (Marchand 1908). Trommsdorf (1906) further believed he showed in such animals a decreased motility and phagocytic activity of the leucocytes and a diminished capacity for regeneration of alexine and for elaboration of specific antibodies. (For literature on this subject, see Foord, 1918.) But, as

Marchand himself says, and as our experiments would indicate (see below), no such considerable lowering of body temperature occurs in the great majority of instances of exposure responsible for excitation of the common upper respiratory infections. Conditions in the existing animal experiments are not properly comparable to the conditions of "catching cold" in man; we must look elsewhere for an explanation.

The theory commonly advanced has been that cutaneous chilling, driving the blood inward, produces, by mechanical or reflex means, or both, congestion of the internal organs. Indeed such congestion has been demonstrated in animal experiments by a number of authors: Lassar (1880) sectioned the lungs, livers and hearts of animals after immersion in ice water, and found their vessels greatly dilated. Schüller (1881) has shown congestion of the arteries and veins of the pia mater in animals chilled by application of cold compresses. Rossbach (1901), Kisskalt (1901) and others have made similar observations upon the epithelium of the exposed trachea. Winternitz (1881) has demonstrated an increase in the volume of the arm of a human subject immersed in a cold sitz-bath, a decrease in the arm's volume when the bath-water was warm.

Many authors have assumed that such findings apply equally well to the human nose and throat. The common observation that chilling may in a few minutes be followed by a feeling of stuffiness in the nose, has seemed to lend plausibility to such an assumption. That it is nevertheless abolutely at variance with what actually occurs in the nasal cavity, nasopharynx, oropharynx, tonsils and palate is shown by the experiments to be described below.

EXPERIMENTAL STUDIES OF VASOMOTOR REACTIONS OF HUMAN SUBJECTS TO CHILLING OF THE BODY SURFACE

Inquiry as to how the human upper respiratory mucous membranes are affected by chilling of the body surface has been undertaken by the present authors by methods of their own devising. (Mudd and Grant, 1919; Grant, Mudd and Goldman, 1920.) The mucous membranes of the palate, faucial tonsils, oropharynx and nasopharynx and of the nasal cavity have been studied, primarily with regard to the vasomotor changes reflexly effected in them by chilling; and in the more recent work the changes in the bacterial flora occurring during the chilling experiments have also been considered.

Methods. The experiments were performed upon human subject, for the most part third and fourth year medical students and recent graduates.

Of the several criteria of vascular condition, *heat* seemed most readily susceptible of quantitative study. Estimation by inspection of the *redness* of the mucosæ was used as a check.

To follow superficial temperature changes in the sites under consideration by the direct application of thermometers was quite impracticable. Thermogalvanometry was of necessity employed therefore.

Apparatus used: Two similar three-element thermopiles were made up of German silver wire, No. 30. and of copper wire, No. 25. In making each thermopile, three lengths of the German silver wire about a yard long were soldered alternately to three pieces of copper wire of the same length. The wires were then folded together to make a single bundle of six strands with three German

silver-copper junctions at one end for application to the surface of unknown temperature, and two junctions and a loose end of copper and another of German silver at the other end of the bundle, which was to be kept at a known temperature. To each of the loose ends was soldered a copper wire leading to a rocking key. The known-temperature end of the thermopile was packed in cotton with a sensitive thermometer in a test tube suspended in the room by a clamp about its neck, or packed in a thermos bottle containing ice water.

A second three-element thermopile was similarly arranged and connected to the rocking key. From this key copper wires were led to a D'Arsonval galvanometer. Thus, by pushing down, successively, the two ends of the rocking key, each of the thermopiles could be brought successively and separately into circuit with the galvanometer.

The unknown-temperature end of the mucous membrane thermopile, when applied, was continuously bathed in mucus, containing electrolytes. Its terminals had therefore to be insulated from each other; this was accomplished by dipping them repeatedly into an alcoholic solution of shellac. The skin thermopile was similarly protected against short circuiting by sweat. The adequacy of the insulation was proved by calibrating the thermopile both in salt solution and in distilled water.

The sensitivity of the apparatus above described was such that one millimeter deflection on the galvanometer scale indicated a temperature difference of about one-tenth degree centigrade between the two ends of the thermopile in the circuit.

For calibration, the unknown-temperature terminals of the thermopile were bound with elastic about the bulb of a sensitive thermometer and this was immersed in a suspended test tube of distilled water or salt solution.

This test tube was again suspended in a beaker of water containing a stirrer. The temperature of the outer beaker was slightly raised at intervals, the water in beaker and test tube stirred until a constant temperature had been reached, and the thermometer and galvanometer readings then taken. The calibration curves constructed from the data thus obtained were found to deviate appreciably, though very slightly, from straight lines. Temperatures were therefore taken from the curves directly.

Application of the thermopile terminals: The phase of the thermogalvanometric study of the skin and mucous surfaces which presented a new problem was that of applying the unknown temperature ends of the thermopiles. They had to be so fixed upon the site to be studied that they would remain in unchanged position, under constant and light pressure, and in such a way as not to interfere with the rise and fall of temperature in the surfaces under them in response to changing vasomotor conditions. The first two requirements were met by fastening the thermopile wires upon stiff carriers which we may designate as "applicators," and then, in the early work, fastening the latter to the appropriate surfaces by strips of adhesive plaster. Various applicators of carved wood and of wood padded with cotton covered with adhesive plaster were tried and rejected because they interfered with the normal loss of heat from the surfaces under them. Applicators satisfactory in all respects were finally made

from galvanized iron wire. A medium size was used, such that it could be twisted and hammered into the required shapes, yet would bear considerable pressure without deformation. No. 13 wire proved most satisfactory.

The several applicators used in the experiments to be considered below are shown in Figs. 1 and 2. Each consists of a body along which the thermopile

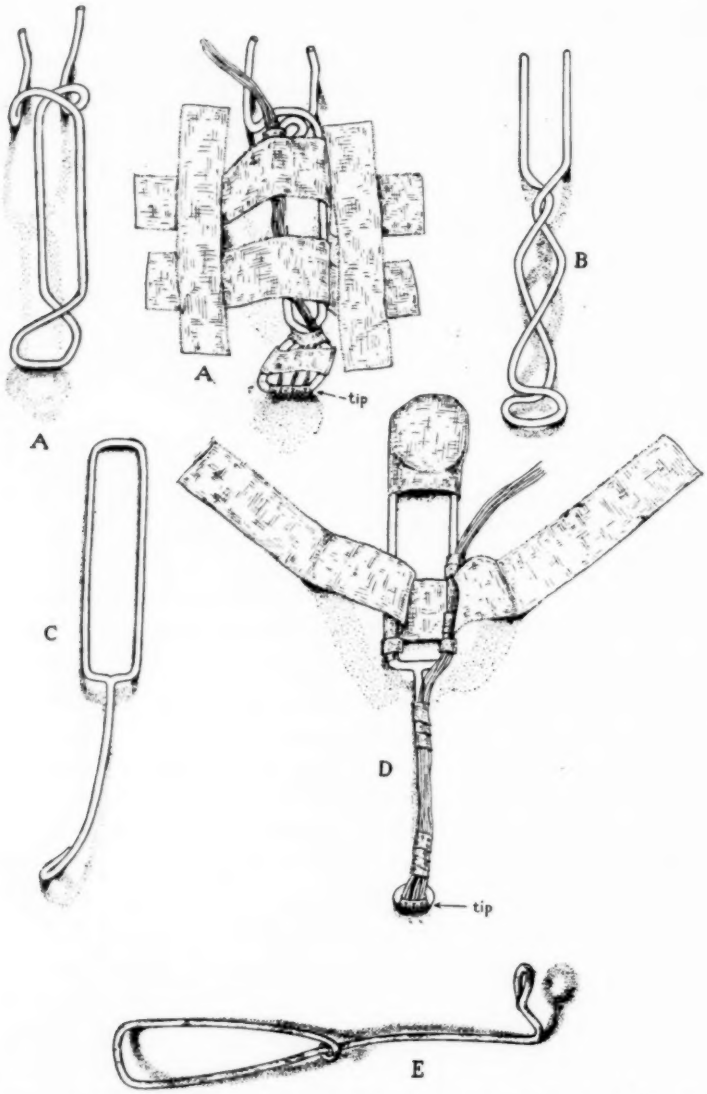

Fig. 1.—Applicators. *A*, for skin; *A'*, same, applied; *B*, for soft palate; *C*, for faucial tonsils; *D*, for oropharynx, ready for application; *E*, for nasopharynx.

wires are strung and supports placed, and a tip just large enough to allow the three terminals of the thermopile to be twisted around it. The tip is so shaped as to conform to the contour of the surface against which it is to hold the thermopile terminals. The terminals, although insulated with shellac as described above, are separated from the metal tip by a single strip of adhesive

plaster as a further safeguard against short-circuiting. (See Fig. 1, *A'* and *D* and Fig. 2, *F*.

The skin applicators (Fig. 1, *A* and *A'*) are so shaped as to form a bridge, resting stably on a support at either end, one of which is the tip, bearing the terminals. Across this raised bridge are placed the adhesive straps which hold the device in position on the skin. The tip rested usually either in the subject's supraclavicular fossa or on the forehead.

The mucous-membrane applicators (Fig. 1, *B, C, D* and *E*) were slung in the subject's open mouth by a long adhesive strip (Fig. 1, *D*), which supported the body of the applicator, then passed up just in front of the corners of the mouth and was fastened on the subject's two cheeks. The tip of the applicator held the thermopile terminals against the particular site on the palate, tonsil or pharynx whose temperature changes were to be studied. The other end of the applicator projected out of the subject's mouth and bore a small weight. Thus

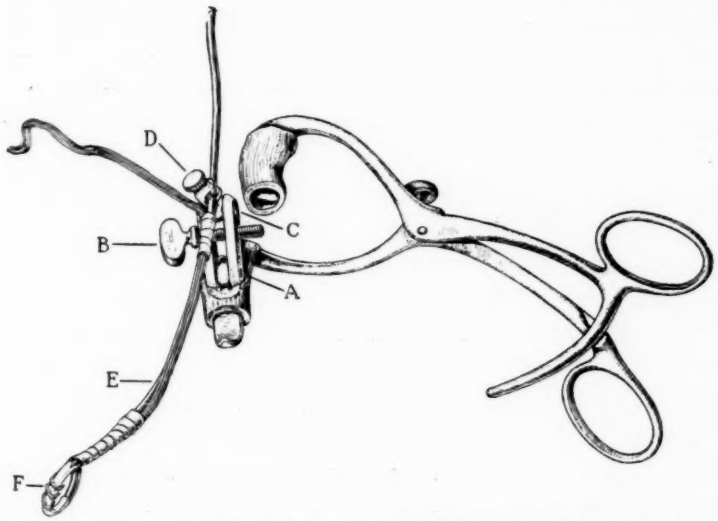

Fig. 2.—Tonsillar applicator and holder. *A* and *C*, ball and socket joints made by metal spheroids and blades of head mirror; *B*, set screw for tightening joints at *A* and *C*; *D*, set screw for fastening applicator in holder; *E*, applicator; *T*, tip bearing thermopile terminals.

the whole device when in position constituted a lever whose fulcrum was the supporting adhesive strip, whose short arm was weighted and the tip of whose long arm held the thermopile end against the mucous surface.

In the experiments upon the faucial tonsils this method was much improved upon. Into one arm of a Doyen mouth gag (Fig. 2) a small brass sphere, *A*, was screwed. A second brass sphere bearing a groove closed by a set screw, *D*, was made. The two spheres were connected by means of the blades of an ordinary head mirror, *C*. The blades could be clamped stably upon the spheres by means of a second set screw, *B*. The applicator, *E*, so shaped as to have its tip fit against the tonsil, was held in place in its groove by the set screw, *D*. By varying the shape and position of the applicator and arranging properly the two joints at *A* and *C* any desired application could be made. The subject's teeth were protected from the metal gag by rubber as shown in the drawing.

The applicator-holder for the nasal cavity experiments consisted of a plate

of strong but slightly flexible fiber-board, about 1.5 mm. in thickness, so shaped that it could be firmly held between the subject's teeth, and cross-hatched with a fine saw to prevent slipping, into which was screwed a metal sphere like that of Fig. 2, *A*, connected through metal blades to a second spheroid with groove and set screw as in Fig. 2. The arrangement of the applicator and thermopile wires was like that of Fig. 2 except that the applicator was straight and its terminal loop for the thermopile tips was very small. The subject held his lips tightly closed over the fiber-board plate.

Arrangement of the subject: The experiments were performed in a constant-temperature room, kept, on the average, between eighteen and nineteen degrees centigrade. The subject entered the room undressed save for shoes and socks, but warmly wrapped in loose garments. Throughout an experiment he sat in unchanging position, tongue held flat on the floor of his mouth, an applicator in position. The sites on which the applicators were placed were of course never wrapped and were protected from direct chilling. The experimenter removed and reapplied the wraps without disturbing the subject. Chilling was effected by (a) removing the wraps, or (b) unwrapping and applying cold wet towels to the subject's back or (c) unwrapping and turning an electric fan upon the subject's back. The third method was found to be by far the most efficacious.

In the earlier experiments very considerable difficulty was experienced because of the necessity for swallowing the saliva and mucus secreted in excessive amounts under these circumstances. This difficulty was subsequently minimized by continuously evacuating the liquids in the mouth through a glass tube—the ordinary saliva-ejector tube of the dentists—connected through rubber tubing with a suction pump on a water faucet.

Factors determining superficial temperature changes: The factors determining the temperature changes in the skin and mucous surfaces during the course of an experiment may now readily be understood. The skin is a surface constantly being heated from below by the circulating blood in the cutaneous vessels (and to a less extent by direct conduction of heat from the deeper tissues), and constantly losing heat by evaporation of moisture, and by radiation, conduction and convection to the cold air of the room to which it is exposed. Since the temperature of the room (and of the deeper body tissues) remains virtually constant throughout the experiment, the skin temperature depends primarily upon two variable factors, viz., (a) the blood temperature and (b) the amount of blood per unit of time which circulates through the cutaneous vessels. Of these the latter is incomparably the more important. For although a rise or fall in blood temperature would of course tend to effect a corresponding change in skin temperature, yet such blood-temperature changes under the conditions of our experiments were found to take place only to a relatively slight degree. It is a fact of much greater moment, that, as more blood circulates through the skin, the superficial temperature must rise, that as the cutaneous vessels are constricted the superficial temperature must fall.

For theoretical completeness, alterations in rate of evaporation of sweat must also be considered. However, with the sudden changes from warmth to chilling and vice versa

used in our experiments, sweat evaporation changes must have played a small part; and whatever part they did play must have been simply to make less striking the primarily important effects of vasoconstriction and vasodilation. For example, chilling the body surface was found experimentally to cause a sharp fall in superficial temperature due to reflex cutaneous vasoconstriction. But this same chilling would decrease the production of sweat and the rate of sweat evaporation and hence tend to prevent the fall in temperature incident to vasoconstriction; and similarly for warming the body, *mutatis mutandis*.

Also in the mucous membranes the factor of prime importance in effecting temperature changes is that of vasomotor tone. Blood temperature, because of its relative constancy, is of minor interest. Room temperature, rate of evaporation of liquids and conduction of heat to the surface from deeper tissues are all virtually constant throughout the experiment, and so require no consideration. A third factor of consequence operating here must, however, be considered—namely, changes in rate and volume of respiration. We may assume the mucous membrane, warmed by the circulating blood, to be losing heat in three ways, (a) by direct radiation through the open mouth, (b) by inhalation of cool air

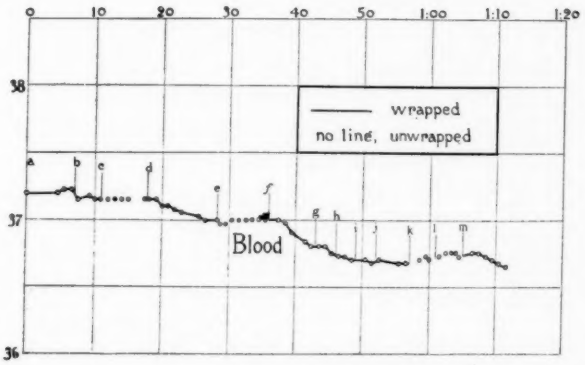

Fig 3.—Blood temperature control. *a*, electric light is reflected on thermometer, *b*, light removed; *c*, unwrapped; *d*, wrapped; *e*, unwrapped, fan on; *f*, fan off, wrapped; *g*, muscles of subject under tension; *h*, subject feels warm; *i*, subject sits comfortably, skin seems flushed; *j*, subject feels cold; *k*, unwrapped, cold towels to back; *l*, fresh cold wet towels to back; *m*, dried and wrapped.

and exhalation of warm air in respiration, and (c) by conduction down a thermal gradient established through the air in the mouth, and especially along the metal applicator, to the cold room outside. From what has been said above it is evident that the rate of heat loss by (a) radiation, and (c) conduction was kept virtually constant throughout each experiment. In all the experiments cited below (b) respiration was carefully controlled—rate by breathing in time with a metronome, and depth by the use of a thoracic and an abdominal pneumograph writing on a smoked drum in sight of the subject.

Finally, the effects of air currents and eddies in the experimental room must be considered. Although the sites of application of the thermopiles were protected from the direct draft of the fan, minor currents and eddies were necessarily set up in the small closed room and the direct cooling effect of these upon the exposed skin could not be eliminated. This direct cooling, as closely as we have been able to estimate it, probably amounted usually to between one-third and one-half of the observed skin temperature fall. The curves should be

studied with this correction in mind. On the other hand it is obvious that in experiments in which the mouth was closed and the applicator upon the pharyngeal wall, currents in the room could not have entered at all into the depression of mucous membrane temperature. Similarly with the applicator in the nasal cavity and nose breathing, or on the palate or pharyngeal wall, even with the mouth open, direct cooling by air currents in the room could have entered but slightly or not at all into the observed mucous membrane temperature fall. The effect of the air currents, then, has been to make appear less striking in comparison with those of the skin the vasoconstrictor reflexes of the mucous membranes with chilling of the body surface.

The thermopiles when applied under the conditions described do not record precisely the absolute temperatures of the surfaces as they would be in the absence of the thermopiles. However, we believe that this method does afford an accurate and sensitive means of recording superficial temperature changes, and, through these, states of vasomotor tone, and it is with these that we are concerned. Measurement of the absolute mucous membrane temperature, if desired, could be effected by a modification of the method used for the skin by Benedict, Miles and Johnson (1919).

Control Experiments: In order to determine the validity of mucous membrane temperature as a criterion of vasomotor tone it was necessary to study changes effected in respiration, blood pressure and blood temperature by the conditions of our experiments. Without going into detail, the results of these control observations may be briefly summarized.

Chilling the body surface has, both in our controls and in animal experiments (Ansiaux 1889, p. 569) increased the volume of respiratory change, and this in turn often depressed mucous membrane temperature. It was for this reason that control of respiration by metronome and pneumographs was necessary.

Blood pressure was not, in the two trials made, significantly altered by chilling. Animal experiments have shown an initial rise, followed, in instances of extreme chilling with depression of blood temperature, by a progressive fall (Marchand, 1908, p. 125, and Ansiaux, 1889). The depression of superficial temperature observed with cutaneous chilling was therefore not the result of lowered blood pressure.

Blood temperature, as has been said, underwent only slight alterations during the course of our experiments. So efficient is the heat regulating mechanism in man, indeed, that during chilling the blood temperature rose very slightly, to undergo a slight fall on cessation of chilling. (Fig. 3.) Liebermeister (1860) found essentially similar changes in axillary temperature with chilling of the skin.

(To be continued.)

UNSUCCESSFUL RESULT FOLLOWING TRANSFUSION WITH IMMUNIZED BLOOD IN A CASE OF INFECTIOUS ENDOCARDITIS

By Louis A. Levison, M.D., Toledo, Ohio

THE treatment of various infectious processes by the transfusion of blood taken from donors who have been immunized against the bacterial agent involved has introduced a new therapeutic procedure that is now on trial. Within recent years there have been several reports of such cases by various observers, but the scarcity of these instances and the variable circumstances under which they have been managed renders a conclusion in regard to their value very difficult. Conclusions based upon individual case reports are notoriously unreliable.

An instance of a successful result from the transfusion of immunized blood was reported by Little[1] who cites the case of a girl of eleven with epidemic influenza complicated by laryngitis, pleurisy, suppurative glossitis and finally a general septicopyemia with the isolation of a staphylococcus and an unidentified bacillus from the blood. A vaccine was made and a donor immunized by giving an injection prior to the last two transfusions. In all four transfusions were given. The septic temperature disappeared and the patient recovered. It was the belief of Little that this therapeutic procedure was life saving in this instance.

CASE REPORT

W. R., age twenty-one, occupation college student, unmarried.

Family History.—Father and mother both living and well. Nothing unusual in the history of relatives or antecedents.

Personal History.—Diphtheria at age of two. Patient is a third year student in the University of Michigan and has not been sick during his period of school. In 1918, when examined for military service was found to have a loud systolic murmur at the apex of the heart and was summarily rejected from duty. This murmur was not known to him before and so far as he or the family knew, there had been no trouble in any way from cardiac trouble. Patient did not pursue any strenuous athletic exercises, but ordinary activities were easily carried out.

Present Illness.—The present illness began in March, 1920. There were evidences of a sore throat about this time but no definite attack of acute tonsillitis. The patient was examined several times during this month at the medical clinic of the University of Michigan where a heart lesion and fever were discovered on account of which he was requested to remain in bed for short intervals of time. However the fever was not a continuous one so that he was permitted to leave his bed and resume his student activities. Three times during the month of March there were times when he was confined to his bed with fever for short periods, resuming his work in the intervals. About the first of April the fever became more persistent and he was sent home from school and did not return. Since that time, he has been confined to his bed continuously. Fever was a constant symptom varying from 99½ to 103½. There was no regularity in the temperature curve but the afternoon temperature was generally the higher. The pulse ranged from 100 to 120 and the respiratory rate was not increased. There was no evidence of cardiac decompensation such as edema, dyspnea or cough. Patient was fairly comfortable while lying quietly in bed. There were no pulmonary

[1]Little: Jour. Am. Med. Assn., lxxiv, 734.

symptoms, and the gastrointestinal tract did not give rise to any unusual trouble, except occasional distress following his food. There were no urinary symptoms. Later certain complications ensued.

Examination.—The patient, at the outset, was of good size, weighing 180 pounds. Emaciation was gradual and steady. Nothing unusual was noted as to the condition of the bones, joints, or lymph glands. The cheeks were flushed. The skin showed a gradually increased pallor with the progress of the disease. There was no delirium. Speech was normal. The tonsils were large, spongy and showed yellow deposits filling some of the crypts. This condition persisted throughout the course of the disease. Teeth were good, throat showed a chronic pharyngitis. Neck: Thyroid not enlarged. A distinct pulsation was felt in suprasternal notch, coinciding with the systole of the heart. The carotid pulsation in the neck was throbbing and violent and could be seen from a considerable distance.

Heart.—Inspection showed a waving apex impulse extending to the anterior axillary line. No thrill on palpation. Percussion showed heart dullness, increased transversely, and also a slight widening of the aortic dullness. There was a loud systolic murmur to be heard all over the precordium and also in the left axilla, left back and the first and second interspaces of either side. There was also a diastolic murmur heard at the base of the heart. The first sound was distinctly heard, but was gradually replaced by the systolic murmur. The second sound at the base was faintly heard. The radial pulse was equal on the two sides. Blood pressure at the outset was 120/0. Later the systolic pressure dropped gradually to 90 and a short time before the end to 80. There could be heard at all times a distinct note on auscultation over the brachial artery during diastole. A capillary pulsation was noted.

Abdomen.—Liver and spleen were not large and could not be palpated. There was moderate tenderness over the epigastrium during the periods when he had gastric distress, but no other abdominal findings. The genitourinary apparatus was negative.

Laboratory Findings.—The urine was dark yellow in color, acid specific gravity ranging from 1016 to 1022, albumin present in small amounts at intervals, no sugar. Granular casts were occasionally seen with a few red cells and leucocytes.

Blood.—Red count decreased gradually from 4,100,000 downward, but the figure varied considerable on account of repeated transfusions. The white count before transfusion varied from 18,000 to 22,000. The percentage of polynuclears was 88 per cent. Blood culture showed a pure growth of streptococcus viridans. (Dr. Pamment). Blood group II. Wassermann reaction negative.

Course of Disease.—During the course of the disease, which extended from April until July inclusive, there were several complications which appeared. Towards the latter part of June the left hip become very much swollen, apparently fluctuating, and excruciatingly painful. Morphine was required to allay this pain. It was thought that pus was present and repeated aspirations were made. However, no fluid was found excepting small amounts of blood. It is probable that this condition was caused by a hemorrhage into the hip joint and surrounding tissue. Later there was an embolus in the left lung with the sudden onset of cough, bloody sputum and an increased respiratory rate. This cough and bloody sputum persisted until the end.

Treatment.—In the absence of any specific treatment for infectious endocarditis, symptomatic measures were employed throughout the illness. Injections of sodium cacodylate were without apparent effect. Intravenous injections of electrargol were employed also without apparent result. It was decided after the isolation of the streptococcus from the blood to prepare a vaccine from this organism, immunize a donor (Group II) and give the patient repeated blood transfusions from this immunized blood. A donor was selected in the person of a healthy, stout, maternal uncle, weighing 200 pounds. He was given repeated injections of vaccine prior to the first transfusion and continued throughout at intervals of four days. Four transfusions were done by the citrate method employing 500 to 600 c.c. of blood at each injection. In all 2200 c.c. of blood were transfused within a period of five weeks. Following the first transfusion there was a moderately severe reaction with a chill and rise in fever, but these reactions practically disappeared after the later ones. The

result of the transfusions was to increase the hemoglobin content of the blood, raise the number of red cells, lower the number of leucocytes and decrease the percentage of polymorphonuclear cells. The strength of the patient was maintained by this procedure to a marked degree. However there was no definite change in temperature curve following any of the transfusions. At no time did the temperature remain normal for the duration of even one day. The pulse rate was not reduced. The hemorrhage in the hip joint and the embolism into the lung occurred during the period of time in which the transfusions were being employed, but did not directly follow any of them. On July 8 the temperature dropped to normal, but with it there was an increase of the pulse rate to 140. Patient became weaker and the pulse irregular. Exitus occurred on July 10 with the patient comatose and the heart in fibrillation.

My suggestion that immunized blood transfusions be employed in this instance was concurred in by Dr. C. F. Hoover of Cleveland, who stated that this procedure was a logical one theoretically. In view of the desperate nature of the patient's illness and the entire absence of known therapeutic aid, the patient was very willing to have the experiment attempted. The fact that the donor received the vaccine five times before the first transfusion with a reaction following each injection consisting of a temperature rise, chill, malaise, and an increase in leucocytes is evidence that the donor did respond to the vaccine or in other words was "immunized." The vaccine injections were continued in the case of the donor throughout the intervals between the transfusions. Whatever antibodies might have been produced by this procedure were introduced into the patient in the course of the subsequent transfusions. The experiment was carefully observed and it can be said that beyond the maintenance of the patient's strength and the relief of the anemia that the transfusions were of no avail.

JAMES THEORY OF THE EMOTIONS IN RELATION TO THE ADRENAL GLANDS

By Charles E. Kieley, Cincinnati, Ohio

JAMES postulates that we cannot experience an emotion unless we also experience the physical changes that habitually accompany it. He states his postulate even so boldly as; "We are afraid because we run" rather than "We run because we are afraid." Cannon and his collaborators attempted to show that the physical concomitants of fear were produced through psychic stimulation of the adrenal glands. Accepting both theories it follows that a blocking of the adrenal hyperactivity should prevent the experience of fear. Biedle states that there is but one known substance which neutralizes adrenalin physiologically at all points. This is apocodeine, a drug bearing the same relation to codeine as apomorphine to morphine but not exhibiting the same pharmacologic action as apomorphine. Apocodeine was first prepared by Matthieson and Wright in 1870. It was admitted to the British Pharmacopeia of 1890 as a hypodermic cathartic, but is now almost obsolete, though recommended lately for various intestinal conditions. The subjects for the present therapeutic tests were both psychasthenics whose most prominent symptom was fear.

Miss X is now thirty. She came under my care in 1916. The chief complaint was fear of death. Long and persistent questioning finally showed the fear to have its basis in her religious attitude toward her erotic desires. At five she recalls masturbation by contact with furniture. At eight, and again at thirteen, she submitted to sexual relations by an older cousin, but denies physical indulgence of any kind since then. She is a fervent member of a religion which teaches that to entertain sexual fantasies is as great a sin as physical indulgence and the guilty will be eternally punished. This is the psychic mechanism which determines the fear of death.

Physical examination of the girl has been exceptionally minute and frequently repeated without showing any very definite organic disease. She has always a marked tachycardia, the pulse ranging from 90 to 120 while sitting. She has polakyuria but this is voluntary as she experiences greater eroticism if she allows her bladder to become even moderately full. There is an unexplained inequality of the pupils. Gynecologic examination has shown a hypertrophy of the labia minora. Cystoscopy has twice been negative. Innumerable cardiac examinations have shown no organic lesion. Every conceivable form of therapy has been tried—sedative drugs, rest cure, suggestion and glandular extracts. Suspicious teeth have been removed and (without my advice) a curettage performed. Not the least effect has been noted. Finally I have given her hypodermically from 1 to 2 c.c. of 1 per cent apocodeine solution every other day until 20 injections were reached. She did not experience even the slightest temporary alleviation of her anxiety.

Mr. Y is thirty-five. His past history shows as significant for psychoneurotic disease, only a skull fracture thirteen years ago, which has left him deaf in both ears. During the influenza epidemic he was advised to drink whiskey for prophylaxis. For three months he had one or two drinks a day and dates his fears from that time. His phobia is mainly that of committing suicide. He is well satisfied with life and has no desire for death but is obsessed with a fear of self-destruction. This man has been given 15 injections of 1 per cent apocodeine ranging from 1 to 2 c.c. As in the previous case there has never been any sense of relief from the fear.

CONCLUSION

Granting that Cannon's contention in regard to the bodily effects of fear is correct, the two experiments presented here indicate that an emotion can be experienced independently of the physical changes which habitually accompany it.

A PRELIMINARY REPORT ON BLOOD COAGULATION*

By E. C. Mason, M.D., Cincinnati, Ohio

INTRODUCTION

THE generally accepted interpretation of blood coagulation makes it necessary to use some eight or nine terms, such as, prothrombin, thrombin, proantithrombin, antithrombin, thrombokinase, etc. These terms are used only to name conditions and furnish no light on the true nature of the clotting. Most, if not all, of these terms are given to substances that have been isolated through laboratory methods which furnish products never present at the time of normal clotting.

Several years ago, while studying the nature of the clot formed in human and cow's milk, I was impressed by the action exerted by certain protective colloids. I observed that such colloids made the casein more resistant to precipitating agents, and also that the clot, formed in their presence, was of a different nature. Such protective colloid substances have been used for years in the modification of cow's milk for infants;[1] however, the method of their action was not completely understood. Alexander,[2] in his splendid work on this subject, has demonstrated that the lactalbumin stabilizes and protects casein from coagulation by acid and rennin. With a knowledge of these results, and realizing that the process of milk coagulation is, in many respects, similar to the process of blood coagulation, I conceived the idea that protective colloids probably played a part in blood coagulation. I have been making a study of blood coagulation, with this in mind, and have briefly outlined my observations in the following paragraphs.

ANALYSIS OF THE CLOTTING PROCESS

The fewer the terms used, the less chance for confusion. Therefore I have restricted myself to three. They are; fibrinogen, calcium and phospholipin complex. Of the three factors mentioned, it is certain that fibrinogen and calcium are present in the plasma of the circulating blood. The question arises as to whether or not the phospholipin complex is present, and if present, is it in some inactive form. There is convincing evidence[3] that such compounds are present, in the circulating blood, in the inactive form.

The present plan considers that after the protective influence is removed from the phospholipin complex, coagulation is the result of the combination of the three substances in the diagram; that is, phospholipin, calcium and the precipitating portion of fibrinogen, and the final clot contains these portions. The calcium (salt) probably binds to the phosphorus in place of the protective portion, and the other bond of calcium binds the fibrinogen portion.

I present the following scheme, which I believe will enable one to understand

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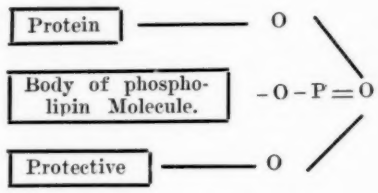
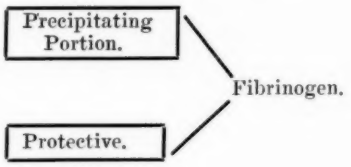
the process. I have used one phosphorus atom as the nucleus, but considering the usual formula for this type of compounds, I should doubtless have used more than one.

(1). Diagram of Phospholipin Complex



(2). Calcium Ca. (salt).

(3). Diagram of Fibrinogen



EVIDENCE THAT FIBRINOGEN SPLITS IN THE PROCESS OF CLOTTING

The main question seems to be, whether fibrin pre-exists in the circulating plasma maintained in solution by other proteins (colloids), and this equilibrium disturbed at the time of coagulation; or is a soluble protein, fibrinogen, *in some unknown manner* converted at the time of coagulation to an "insoluble" product, fibrin. The last view is the one generally accepted. However, the view was strongly attacked by Wooldridge, and the objections which he advanced apparently have not been answered.

Throughout our discussion fibrinogen is spoken of as made up of two portions, (1) the protective portion and (2) the portion capable of being "precipitated." To illustrate the two portions represented in fibrinogen, I have selected, for the sake of simplicity, a fat such as stearin (glyceryl-stearate), the characteristic reactions of which are common to *fibrinogen* and *caseinogen*.

First. The acid treatment of each yields the "insoluble" hydrogen precipitate.

Second. The sodium salt of each is "soluble." It is also possessed of a high hydration capacity.

Third. The calcium salt of each is "insoluble," and this compound has a low hydration capacity.

Fourth. If stearin (glyceryl-stearate) is treated with a calcium salt, no "precipitation" of calcium stearate occurs, but if first treated with sodium hydrate, and then with a calcium salt, the calcium stearate is formed. This is also true of fibrinogen.

Fifth. If compounds such as glyceryl-stearate are treated with sodium chloride, there is no apparent reaction, but if the hydrogen stearate (stearic acid) is treated with sodium chloride, there is an interchange with the formation of some sodium stearate, which is "soluble."

Sixth. The function of the catalytic agent, or "enzyme," is to split each into the two portions.

The work of Hammarsten,[4] Schmiedeberg,[5] Heubner[6] and others, shows that in the transformation of fibrinogen to fibrin a globulin is split off. This is termed *fibrino-globulin* by Hammarsten and serum-globulin by others.

Evidence that compounds such as give rise to "thrombin," remain in the tissues (including blood as a tissue) in the protected form, and if such protection is removed they combine in the formation of the final clot.

The chemical nature of the substance which is active in promoting the fibrin formation (thrombin), has been studied by various investigators. Halliburton[7] and Pekelharing[8] isolated a body from Schmidt's extract which gave proteid reactions, and resembled the globulins in many particulars. At first they classified it as a globulin,[9] subsequently both recognized that the substance was not a globulin and classed it as a nucleoproteid.[10] Pekelharing considered that this nucleoprotein in combination with calcium constituted "thrombin," and stated that it could be formed not only from the nucleoproteins of the plasma or serum, but also from the nucleoproteins in the cells of the thymus, testicle, and other glands, by digesting these with calcium chloride, the excess of the calcium salt being afterwards dialyzed off. According to Pekelharing, this combination does not give up the calcium when dialyzed, nor is the combination broken up by soluble oxalates, although if these are present from the first, they may prevent the original union. Howell, after much careful work on this subject, has stated the following:[11] "My own opinion is that thrombin is a protein or protein derivative."

It appears evident that the function of the calcium, in the process of blood coagulation, is to activate the thrombin, and that there is something present in the normal blood which prevents this action of calcium. For the want of a better name I have termed this the *protective portion*. Various substances, including tissue extract and cephalin, are capable of removing this protective portion, and as a result, calcium activates the thrombin when clotting takes place.[12] "It would seem quite possible or probable that these fibrin-aggregates represent in fact a real physicochemical combination between fibrinogen and thrombin."

Rettger[13] and Howell[14] have definitely shown that there is a combination of the thrombin and fibrinogen in the clotting process, demonstrating that definite amounts of thrombin yield definite amounts of fibrin. Wooldridge's[15] analyses also show that fibrin contains a large percentage of phospholipins. Such phospholipins are not taken into consideration in the ordinary analysis of fibrin, as they are removed from the normal clot by extraction with ether or alcohol.

Howell[16] has shown that the active principle of tissue extract is a phospholipin protein compound, and, as indicated by the work of Pekelharing, tissue extract when treated with a calcium salt will act as thrombin. Therefore, with these two points in mind, I have selected the complex which is presented in the diagram of the clotting process. However, the exact chemical formula need not be seriously considered, for that could vary greatly and the working plan still hold.

Apparently the normal clot is the union of the three substances, and at present I am engaged in finding out the effect produced on the hydration capacity of this system, as the result of varying the amount of each present.

SUBSTANCES WHICH RETARD THE COAGULATION OF BLOOD

Substances retard the coagulation of blood by doing the following:

First. Increasing the protective portion of the phospholipin complex (antithrombin).

Second. Preventing the splitting off of the protective portion of either the phospholipin complex or fibrinogen.

Third. By removing any one of the three factors.

Any condition which will increase the amount of the protective colloid (antithrombin), will retard the coagulation. *Such conditions are realized in the autolysis of tissues of the body, including the white cells.* Evidence for this statement will be found in the observations of the following men: Doyon[17], Wells,[18] Conradi,[19] Whipple,[20] Erben,[21] Pfeiffer,[22] Minot and Denny,[23] Opie,[24] Bell,[25] Dienst[26] and Doehez.[27]

SUBSTANCES WHICH ACCELERATE THE COAGULATION OF BLOOD

Substances accelerate the coagulation of blood by doing the following:

First. By removing the protective portion of the phospholipin complex.

Second. By contributing reactive material, (one of the three factors presented in the diagram of coagulation, the degree of acceleration depending on the factor increased).

The following substances accelerate the coagulation of blood by one of the two methods just mentioned:

(1). Glass vessels, finely divided glass, glass wool, clay filters, absorbent cotton, etc. (2). Certain synthetic colloids. (3). Electric current. (4). Injured tissue and tissue extracts. (5). Cephalin. (6). Carbon dioxide and acetic acid in the negative phase of coagulation produced by peptone injection.

These substances all have one point in common, being *electro-negative.* This property apparently plays a very active part in their reaction, for if the charge is reversed, as in the synthetic colloids prepared by Grimaux,[28] they lose their activity. Again as in the case of the electric current,[29] coagulation takes place at the pole which accumulates negative charges.

Apparently the protective portion of the phospholipin complex is either neutralized, or its place satisfied by reacting with electro-negative substances.

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AN ANALYSIS OF ONE HUNDRED POSTMORTEM EXAMINATIONS IN SIAM*

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MEDICAL literature has so few references to conditions in Siam that I believe statistics of 100 consecutive postmortems are of sufficient clinical and pathologic interest to merit publication. These were the first made by me in Bangkok and were performed in Siriraj Hospital between August 1, 1919, and June 10, 1920. Twenty-two additional ones were made by other members of the laboratory staff, but are not here included because the records are incomplete. During this period there were 270 deaths in the hospital, which gives a total of 122 postmortems in 270 cases, or 45 per cent. This percentage compares very favorably with that in the United States, where, judging from my own knowledge and from medical literature appearing since I left, things are not entirely satisfactory.

It has been highly gratifying to me during the year to note the number of articles calling attention to undesirable conditions regarding the number of postmortems and the teaching of pathology therefrom. Discussion of this means improvement. If real efforts are made to locate the cause it will doubtless be found that in most hospitals the small number of postmortems is due to remediable conditions. Then let the remedy be applied. For there can be no better place than the postmortem table for the student to learn pathology and for the clinician to check up his diagnoses. And the physician in charge of the case should attend with his Senior students who have studied the patient in the hospital. In my opinion the attending physician should do the greater part of the teaching at this time. The pathologist should point out the morbid anatomy of the lesions and in the light of these the physician can

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discuss with the students the physical signs and the symptoms that had previously been noted. The student must not come away from a postmortem remembering simply that he saw a diseased heart, or a pneumonic lung, or a cirrhotic liver; in addition he must place these facts as the final points of knowledge regarding an individual case of a certain disease. The physician who has been studying the case can aid the students in properly placing these facts; the pathologist can do relatively little. Sending to the postmortem room the history, with or without the interne who wrote it, is an aid but it is an extremely poor substitute for the physician who is teaching the students medicine. If this team work by pathologist and clinician were properly developed, both, as well as the students, would benefit greatly thereby. Each would learn from the other and there would be less petty fault-finding and criticism about each other's work.

Of the 100 cases here recorded, 64 were males, 36 females. Most were Siamese, but Chinese were included.

The ages ranged from stillborn to 67 years. In ten-year periods they were as follows:

Under 10 years	11
From 10 to 19 years	5
" 20 " 29 "	23
" 30 " 39 "	17
" 40 " 49 "	10
" 50 " 59 "	17
" 60 " 67 "	5
Age not recorded	12
	100

The lesions in the cases as recorded in the gross diagnoses varied in number from three to fourteen. The primary or chief cause of death as determined from these and the clinical course of the disease was the following:

Abscess of liver, amebic	1
Abscess of pelvis	3
Appendicitis, gangrenous	1
Atelectasis of lungs	1
Bronchial asthma	1
Bronchopneumonia	5
Calculus of bladder (cystitis)	2
Carcinoma of liver	1
Carcinoma of stomach	1
Carcinoma of uterus	1
Cholera	3
Cholecystitis, suppurative	1
Cirrhosis of liver, atrophic	5
Dysentery, amebic	17
Dysentery, type doubtful	3
Endocarditis, acute	2
Endocarditis, chronic	1
Endometritis, puerperal	3

Edema of brain	1
Fatty degeneration of heart	3
Fracture of skull	2
Gangrene of lung	1
Gastroenteritis, chronic	1
Gunshot wound of abdomen	1
Heat exhaustion	1
Hypernephroma of kidney	1
Influenza-pneumonia	2
Knife wounds	2
Lobar pneumonia	1
Lymphosarcoma (duodenum)	1
Malformation of heart and vessels	1
Meningitis (tuberculous)	1
Mercurial poisoning	1
Myocarditis (chronic)	3
Nephritis (suppurative)	2
Opium poisoning	1
Rupture of uterus	1
Sarcoma of (Liver)	1
Septicemia	2
Syphilis	2
Suffocation (newborn)	1
Tuberculosis (lungs)	10
Tuberculosis (hip)	1
Typhoid fever	3
Uncinariasis	1
	100

This table serves to show the wide range of cases making up the series and also brings out one point worthy of special mention, namely, that 27 deaths (more than one-fourth the total) were due to diseases of the intestines. These were:

Dysentery (colitis)	20
Cholera	3
Typhoid fever	3
Uncinariasis	1
	27

This emphasizes a well-known fact, namely, the high mortality rate in tropical countries from intestinal diseases. These are due almost entirely to bacterial or parasitic contamination, primarily of soil or water, and secondarily of the food supply. The almost constant high temperature of such countries favors the continuous growth of animal parasites and bacteria which in colder climates are checked or for a time prohibited by periodic freezing of the ground. This, aided by common methods of soil fertilization (by human excrement) furnishes a prolific source of disease. It is a point constantly to be emphasized about the tropics to medical students and physicians, especially those engaged in Public Health service. The latter have particularly difficult conditions with which to deal in the prevention of disease.

Some of the findings in these cases, as will be noted later, belong to the rarer lesions but most of the cases were of the more common ones that are especially valuable to students. I believe that we as teachers too often spend on rare cases time that could be much better employed on the fundamentals of common ones. It is true that unusual cases are always deeply interesting to the teacher and are of great value in medical literature. They must also be brought to the attention of the student but of the time of the latter they require only a minimum. Many of the conditions here recorded were found just at the right time to illustrate topics of the lecture course and thus to quite a degree helped atone for the scarcity of museum specimens. In none of my many series of 100 postmortems has there been one with more cases of real teaching value.

Before taking up in detail some of the points brought out by this series, I wish to give a summary of the lesions in the chief organs. This will also give an idea of the frequency with which the various organs were diseased. Of course a series of 100 cases is not large enough from which to draw lasting conclusions as to frequency of a certain condition. It will, however, give a general idea of the findings here as compared with those in the United States.

HEART:

- Aneurism, 1
- Atrophy, 2
- Brown atrophy, 1
- Dilatation
  - Left ventricle, 19
  - Right ventricle, 13
  - Left auricle, 3
  - Right auricle, 13
- Endocarditis
  - Mitral
    - acute, 3
    - chronic, 1
  - Aortic
    - acute, 1
    - chronic, 2
  - Mural, 1
- Degeneration
  - Fatty, 18
  - Parenchymatous, 31
- Hypertrophy
  - Left ventricle, 5
  - Right ventricle, 5
- Malformation, 1
- Malposition, 1
- Myocarditis, fibrous, 21
- Patulous foramen ovale, 7
- Tumor, secondary, 1

ARTERIES:

- Absence of pulmonary, 1
- Aneurism of aorta, 1
- Arteriosclerosis
  - General, 1
  - Aorta, 10
  - Coronary arteries, 3
  - Syphilitic
    - Aorta, 3
    - Pulmonary, 1

LUNGS:

- Abscess, 3
- Atelectasis, 7
- Bronchiectasis, 1
- Bronchitis
  - Acute, 17
  - Chronic, 3
- Congestion, 47
- Edema, 30

- Emphysema
  - Vesicular, 43
  - Interstitial, 2
  - Interlobular. 1
- Gangrene, 1
- Infarct, 3
- Malformation, 3
- Pneumonia
  - Lobar, 1
  - Broncho
    - Left, 9
    - Right, 7
  - Chronic interstitial, 2
- Tuberculosis
  - Active
    - Left, 10
    - Right, 7
  - Healed
    - Left, 6
    - Right, 7
- Tumor, secondary, 1

PLEURAE:

- Hemothorax, 3
- Hydrothorax, left, 4; right, 6
- Pleuritis
  - Acute
    - left, nonsuppurative, 2
    - right, nonsuppurative, 4
    - right, suppurative, 1
  - Chronic adhesive
    - left, 25
    - right, 27
- Pneumothorax, 2

SPLEEN:

- Accessory, 14
- Absence, 1
- Atrophy, 5
- Congestion, 23
- Chr. capsulitis, 7
- Chr. splenitis, 7
- Enlargement, 27
- Infaretion, 1
- Pigmentation, 7
- Softening, 8
- Tuberculosis, 2

KIDNEYS:

- Congestion, 17
- Hydronephrosis, 1
- Hypernephroma, 1
- Malformation, 1
- Malposition, 2
- Nephrolithiasis, 1
- Nephritis
  - Parenchymatous
    - acute, 9
    - chronic, 8
  - Diffuse, chronic, 6
  - Interstitial, chronic, 10
  - Suppurative, acute, 3
- Parenchymatous degeneration, 25
- Tuberculosis, 2

STOMACH:

- Carcinoma, 1
- Carcinomatous ulcer, 1
- Congestion, 8
- Gastritis, acute, 1; chronic, 7
- Ulcer, 2

LIVER:

- Abscess, amebic, 3
- Cirrhosis—atrophic, 5; congestive, 8; syphilitic, 1
- Congestion, 39
- Fatty infiltration, 14
- Malformation, 1
- Pigmentation, 4

Parenchymatous degeneration, 27
Tuberculosis, 2
Tumor, angioma, 1; carcinoma, 1; Hypernephroma, 1; sarcoma, 2

INTESTINE:

Duodenum, ulcer, 2; lymphosarcoma, 1
Small intestine: Enteritis, catarrhal, 8; follicular, 3; ulcerative, 4
Stabwound, 1
Tuberculosis, 6
Lipoma, 1
Typhoid lesions, 3
Colon: Colitis, amebic, 17; catarrhal, 4; ulcerative, 6
Tuberculosis, 4
Tumor, 1
Syphilis, 1
Stenosis, 1
Rectum, gangrene, 1

PERITONEUM:

Abscess, appendiceal, 1; pelvic, 2
Ascites, 16
Carcinoma, 2
Peritonitis, acute, 11; chronic adhesive, 8
Tuberculosis, 1

MISCELLANEOUS:

Jaundice, 4
Transposition of viscera, 1
Leukoderma, 1
Fracture of skull, 2
Fracture of humerus, 1
Ascariasis, 2
Uncinariasis, 1
Tapeworm, 1

A very common condition here is vesicular emphysema of the lungs. This was a feature I noticed from the beginning because of its much greater frequency than I had found in the United States. This diagnosis, given in the table as 43 cases, could have been given a greater number of times if note had been made of its evident presence in lungs that had other lesions, as pneumonia, tuberculosis, or congestion and edema. Minor degrees were not recorded as I have come to regard the condition as almost constant here in adults. In many it is of an advanced degree. The type is the essential, or large-lunged, emphysema. Why this is true I do not know. Castellani and Chalmers say that "emphysema and asthma are fairly common in the tropics." I am informed that asthma is quite frequent in this country but do not believe it is so universal as emphysema seems to be. The condition is an interesting one for which I shall seek further explanation.

Some of the other lesions are less frequent than we are accustomed to find them in the United States. The presence of gallstones was noted in two cases; in both they were small and few in number, not at all like the dozens or hundreds as we find them in not a few bodies.

Sclerosis of arteries is less common here. In only one of the cases was the diagnosis of general arteriosclerosis justified, although in several there was sclerosis of certain arteries, as the aorta, coronaries, or renal. In only one case was there extensive involvement of the aorta with large yellow firm patches, a few calcareous. With the extensive amount of salts in the water here and the fre-

quency of bladder calculi, it might be thought that calcareous infiltration of damaged vessels would be frequent. From other observations regarding this condition, I believe it would, were the vessels damaged as so often found in elderly persons in the States.

The rarity of gross syphilitic lesions in spite of the supposed great prevalence of that disease has been a striking point. In the absence of Wassermann tests in the hospital, the number of cases among the one hundred cannot be stated but the postmortem manifestations were not indicative of many. Of the lesions tabulated under vessels and liver, most were in one case, a woman of thirty-six years. This body furnished the syphilitic cirrhosis of liver, arteritis of pulmonary artery and one of the instances of aortic involvement, and the aneurism of the aorta.

Another condition that theoretically should be very often found proved not to be so. This is malarial pigmentation of the liver and spleen, with enlargement of the latter. The table shows 7 cases of pigmentation of the spleen and 4 of the liver. The cases of enlargement of the spleen as tabulated, 27 in number, were mainly those of infectious conditions or congestion due to other well defined diseases. The instances of pigmentation were mostly in moderate-sized organs instead of notably large ones. Not all the spleens were examined microscopically and it may be that more of them were pigmented than the size and color would indicate, but I am speaking now of gross appearances. This is one of the many problems to be investigated in further series of cases. A point to be remembered in this connection is that the large majority of cases in the series were from Bangkok, in which malaria is not nearly so frequent as in the jungle regions further North.

Malformations were not numerous in this series. The most notable was the one with an opening in the interventricular septum of the heart with absence of the pulmonary artery and spleen. These, with accompanying transposition of viscera, made the case a most unusual one. It has been published in the *Journal of the American Medical Association*. This child also had a four-lobed lung on each side; in two other bodies the left lung had partial separation into three lobes. One kidney was moderately changed in shape and was also out of position.

One newborn child had malformations of the external genitals making it worthy of the term hermaphroditism, although it seemed fairly certain a male. The scrotum resembled labia and the rudimentary penis had complete hypospadias. The testicles were found in the abdominal cavity near the brim of the pelvis.

An interesting malformation of the bladder was found in a woman of sixty-five years. This was a diverticulum extending from the right lateral portion. It began as an opening 1.5 cm. in diameter and gradually increased in size to its termination, being 6 cm. long. This sac was entirely empty. The absence of calcareous material is of interest because the pouch would seem to have furnished admirable anatomical conditions for the formation of calculi. Of course women are less liable to this condition than are men.

Finally a peculiar malformation was the condition of the great toes in a man of unknown age. Each was short, only half as long as the second toe of

each foot. It may be said in passing that supernumerary little fingers and thumbs are not of great rarity in Siam, though none of the bodies in this series showed them. Supernumerary mammary glands are also fairly frequent, three cases being in the Obstetric Department of the hospital at one time.

TUBERCULOSIS

Death was attributed to this in 11 cases, 10 of the lungs and one of the hip. In some of the pulmonary cases tissue destruction was very great, cavities occupying the whole of an upper lobe being found. In spite of this, however, the general statement can be made that the process does not appear so widespread, so active, so broadly destructive as in the average case in the United States. The impression gained is that the tissue destruction is spreading slowly. The cavities as a rule have quite smooth walls and many have considerable fibrous tissue in them. Around the cavities may be found small tubercles, but rarely any extensive areas of necrosis. In some cases with a cavity of 2 cm. in diameter, no tubercles are seen near it. In the lower lobes of lungs with extensive cavities in the upper, are often areas of conglomerate tubercles but with very little necrosis in the center. Even in the upper part of such lobes, with small cavities present, necrosis does not appear prominent or active. In cases without extensive destruction (with death due to other causes) I have found cavities of 1 or 2 cm. in size in a lung, with no tubercles whatever around them; in one instance, we examined spreads from the wall, finding it loaded with tubercle bacilli, before I was finally convinced that we were not dealing with an abscess.

Many of these cases had no involvement of spleen, liver, lymphnodes or intestine. Some had tuberculous ulcers of the intestines with numerous tubercles in the serous coat. Of course the disease destroys tissue and causes death but the general appearance is that the tissue has been putting up a good resistance. The duration of the cases I do not know and it may be the clinical history (if it could be obtained accurately) would negative this supposition based on the appearance of the lungs. Whether the cases were of slow progress and long duration or not, the fact remains that the disease was responsible for 11 of the 100 deaths. It should be added that in 11 other bodies there was healed tuberculosis in one or both lungs. This adds to the total number of infections. So far as climate is concerned, Bangkok would seem to be one of the worst for tuberculous persons. It is only four feet above the sea level and during half of the year the air is extremely moist.

INFLUENZA AND PNEUMONIA

Two deaths were attributed to influenza and its complicating lung lesions. One of these clinically was influenza with a duration of 10 days; the lungs were typically like those of the thousands of cases coming to postmortem during the great epidemic of 1918. The other patient was brought to the hospital unconscious and died in 20 hours with no clinical history obtainable. The lung lesion was in a fairly early stage, but I am convinced it was of the same type. Cases of this disease, whatever it should be called (we are calling it influenza),

are occurring here from time to time. In addition to the two cases here reported, one typical case with pneumonia came to postmortem recently at the Chulalongkorn hospital. I think there is no doubt that some cases of common cold, of bronchitis, and of bronchopneumonia are designated influenza. But it is equally certain that sporadic cases of the type of the epidemic of 1918 are occurring; in those developing pneumonia the mortality is high.

BRONCHIAL ASTHMA

This case occurred in a man of fifty-two years who had had attacks since early childhood. His paternal grandmother and father had the disease and one of his children now has it—a family history of four generations. Curschmann's spirals were found in the bronchi. The lungs showed emphysema. The bronchi had an acute catarrhal inflammation. Twelve years ago while in Berlin I had the opportunity of studying and reporting the eighth case in medical literature with microscopic examination of the lungs. This I believe to be the twelfth. These lungs shed no new light on the pathology of the disease, although the duration of the case should have led to chronic changes if any ever occur.

TUMORS

There were 9 cases of tumor, 7 malignant and 2 benign. Of the former, 4 were carcinoma, 2 sarcoma, and 1 hypernephroma. One case of carcinoma of the stomach was in a woman of forty-two. It was of the diffuse type with thickening and ulceration of the entire wall. It extended to the surrounding tissues but gave no metastases to the liver. A squamous-cell epithelioma of the uterine cervix in a woman of sixty-seven had extended to the bladder. A third case in which carcinoma had caused death was in a man of thirty-four. The liver was the organ chiefly affected, being studded by nodules of various sizes. The duodenum was adherent to one of the nodules and when separated was found to have a small perforation, at the base of an ulcer. The case was taken to be one of primary carcinoma of the liver, with multiple nodules from early spread by the veins. Microscopic study of the duodenal lesion showed a chronic ulcer with very thick walls of dense fibrous tissue and in this at one point a few aberrant epithelial cells that may be part of a malignant growth. These cells are too few to make the diagnosis of cancer positive but makes it strongly probable. The case is therefore better regarded as one of chronic ulcer of the duodenum with carcinomatous change and multiple metastases in the liver.

An instance of undoubted carcinomatous change in a chronic ulcer was found in a man of sixty-two years. In the greater curvature of the stomach was an ulcer 6 cm. in diameter, with a nodular elevation in the center that proved to be adenocarcinoma. There were no metastases, death being due to gangrenous cholecystitis.

Of the sarcomas, one was a lymphosarcoma of the duodenum in a woman of thirty-six years, with symptoms of six months' duration. A perforation 3 cm. in diameter had occurred; this was adherent to the gall bladder but leakage had started peritonitis. The second, third, and fourth parts of the duodenum were

an ulcerated, thickened mass of partly necrotic tissue with narrow segments of the lumen. Microscopically the growth was of small round cells and could have been called a small round-cell sarcoma but was so similar to the lymphnodes it infiltrated that the term lymphosarcoma is regarded more appropriate. This belongs to the rarer tumors in this location.

The other sarcoma was also one of infrequent occurrence, a primary sarcoma of the liver. This was in a Chinese woman of thirty-one, with an obscure history as to duration but probably about six months. A large mass with almost parallel sides and a rounded end extended from the lower part of the right lobe of the liver diagonally across the abdomen to a point below and to the left of the umbilicus. A needle puncture gave pure blood. Opening the abdomen revealed an inoperable mass of soft reddish tissue that under great pressure welled out of the incised capsule. Postmortem showed a growth of the liver replacing more than half of the right lobe and extending 15 cm. beyond the border as a cylindrical mass 12 cm. in diameter. The tumor was extensively necrotic with many areas of hemorrhage. There was no tumor elsewhere in the body. Microscopic sections are of round-cell sarcoma.

The other malignant tumor was a hypernephroma 16 cm. in diameter that replaced the upper two-thirds of the right kidney and the adrenal. There were multiple secondary nodules in the liver and lungs.

Of the benign tumors, one was a hemangioma of the liver 3 by 4 cm. in a woman of fifty-four. The other was a lipoma 2 cm. in diameter projecting into the lumen of the middle of the ileum of a woman of 50 years.

TYPHOID FEVER

There were three cases of this disease in males of twenty-one, eighteen, and seven years. The first two mentioned had extensive lesions in the lower six feet of the ileum and both had numerous small ulcers in the cecum. The first had the most marked inflammation of the mucosa of the ileum that I have ever seen in a case. The boy had but little lymphoid tissue in the ileum, therefore but few lesions; there were none in the cecum and the ileum between the ulcers was not inflamed. But the ulcers present were deep and one 10 cm. above the ileocecal valve had perforated and caused peritonitis. Comparison of these cases emphasizes a point of great importance regarding the lesions of this disease, namely, that perforation does not necessarily imply an extensively inflamed or ulcerated intestine. Of these three cases, perforation occurred in the one with the least lymphoid tissue in the intestine, with the shortest length of intestine involved, with the fewest ulcers, and the least inflammatory tissue around the ulcers.

In addition to these three cases of typhoid fever, the ileum of a woman of fifty-one contained bile-stained scars that were probably the remains of lesions from which she had recovered. There have been several other cases of the disease in the hospital during the past year. Typhoid therefore appears to be an endemic disease in Bangkok although some physicians were skeptical about it when I first came. There are so many types of fever in the tropics, many of them of unknown origin, that proof of specific diseases is demanded.

MULTIPLE ANEURISMS OF HEART

These were in a woman of unknown age and formed an instructive instance of the effect of sclerosis of the arteries. One aneurism was a cone-shaped projection 2.5 by 1 cm. at the apex of the left ventricle. At the summit the wall of the sac was formed of pericardium only, but the terminal 1.5 cm. was occupied by a blood clot partly organized into fibrous tissue. This, as fortunately often happens in such cases, undoubtedly prevented rupture of the aneurism. The second aneurism had an opening 2 cm. in diameter leading from a point behind the posterior mitral leaflet. The sac was 4 by 2 cm. in size and was partly filled by partially clotted blood. This sac was also thin. Both were apparently due to local failure of blood supply from occlusion of small branches of the coronary artery. Other effects of arteriosclerosis in this subject were fibrous myocarditis and softening of the brain.

JAUNDICE IN ATROPHIC CIRRHOSIS OF LIVER

Two of the subjects with atrophic cirrhosis of the liver had pronounced jaundice. This condition is rarely marked in so-called atrophic cirrhosis and even in lesser degrees is present in only a small number of cases. Its occurrence in one case was unexplained by any condition that could be found. The subject was a man who had 9 liters of fluid in the peritoneal cavity. The liver was of the "hobnail" variety. The ducts were open. The liver was greenish-yellow.

The second case was in a man with "hobnail" liver and ascites of 10 liters. The jaundice in this case was readily explained. Dense adhesions of the mesocolon to the pedicle of the liver and along the duodenum almost to the pylorus had added obstruction of the bile ducts. The jaundice was thus really obstructive. Edema of the colon in this man was the most intense I have seen. In some segments the wall was 1.2 cm. thick.

LOBAR PNEUMONIA

This affection is very uncommon as compared to the United States during the time of year embraced in these statistics. Although the "cold" season here (it was not below 55 degrees the past winter) causes many mild or even more severe cases of inflammation of the upper respiratory tract, judging from this series it does not lead to pneumonia in any notable number of cases. The one case here noted was in a man of forty who had a number of chronic diseases with the pneumonia as somewhat of a terminal event. It was of the type known as "central" pneumonia.

INTESTINAL PARASITES

The cases of these were as follows: Hookworm, 1; Tapeworm, 1; Ascaris lumbricoides, 2; Entameba histolytica, 17.

The hookworms were found in a boy of sixteen, who had marked anemia of all his organs. One ascaris was found. Examination of this patient's stools

when admitted to the hospital showed the presence in his intestines of hookworms, ascaris, strongyloides, and trichuris.

The tapeworm was found in the intestine of one of the subjects of typhoid fever. It was the saginata in type.

The ascaris was found, in addition to the case mentioned, in a man of sixty-two, previously described as the patient having carcinomatous change in an ulcer of the stomach and suppurative cholecystitis. Two worms were found in the stomach and four in the common bile duct and liver. The latter had apparently wandered into the liver postmortem, as there was no evidence of lesion in the organ. Infestation by this parasite is world-wide, but it is especially frequent in the tropics. Ova are found in the feces of many of the patients admitted to the hospital here.

AMEBIC COLITIS

The fact that 17 cases of amebic dysentery occurred in this series of 100 is sufficient proof of the prevalence of that disease. Of these cases, 10 were men and 7 women. The lesions in the colon varied from superficial necrosis without ulceration to the presence of many large, well-defined ulcers or to deep necrosis of the entire mucous membrane of the colon. Perforation occurred in two cases but adhesions prevented infection of the peritoneum in one; the other terminated in death from peritonitis. It would be tedious to describe all these cases but three may be briefly cited as illustrations.

One of the striking acute cases occurred in a man of fifty-four. He was ill 12 days, having 15 or more stools daily. Emetin hypodermically had no effect. At postmortem the colon was found involved the entire length. There were numerous ulcers from 2 to 8 cm. long. Some had a clean base of red tissue, others were partly covered by necrotic tissue. In some segments the ulcers were very closely placed, in others separated by broad patches of gray, swollen necrotic tissue. Apparently the entire mucosa of the colon had either been lost by ulcer formation or had become necrotic and was still attached. The ulcers as a rule were not excessively deep but 20 cm. from the head of the cecum was one 4 cm. in diameter that had a base of yellow or brown dead tissue, with the peritoneal surface showing the same color. In this area were three small perforations; around them were adhesions but leakage had occurred and peritonitis developed. Microscopic sections of deep ulcers show necrosis of the submucosa or even into the muscle coat. In the deeper necrotic tissue and along its junction with the living are great numbers of amebæ. This case is an example of extensive ulceration.

Another type of involvement was found in a woman of 28. The wall of the cecum was thickened and the whole of its mucosa yellow or greenish in color but still attached and quite firm. This condition became gradually less marked further down in the colon. At points were a few shallow ulcers, but ulceration was not at all a feature. Microscopically necrosis was very superficial and amebæ were not deep in the wall. The submucosa was swollen and contained fibrin. The process also extended 15 cm. into the ileum, involving the mucosa uniformly as in the cecum, and ending abruptly in a perfectly straight line

entirely around the intestine. This was an instance of superficial necrosis of the intestine of the so-called diphtheritic or gangrenous type with very little ulcer formation.

A third type occurred in a man of forty-four years; duration of disease one month. All the mucosa of the colon and in many areas the submucosa also was necrotic and hanging to the wall as soft grayish-yellow shreds. There were no definite ulcers but at points, especially in the sigmoid, the dead tissue was easily detached, leaving a very thin wall. Along the sigmoid the omentum was adherent; there was no actual perforation but this was evidently imminent. At many places in the deeper layer of dead tissue were small areas 0.5 to 1 cm. in diameter of yellow, semifluid, tenacious substance resembling thick pus. In the tip of the cecum the necrosis was more shallow and more like the diphtheritic type. This same condition but to a less marked degree was present in the lower 30 cm. of the ileum. Above this a 15 cm. segment was hyperemic, then necrosis for 15 cm., thus making the lower 60 cm. of the ileum affected.

These three cases may be taken as types or illustrations. The first was one with many ulcers of various sizes, most of them not deep, but one perforating. The other two did not have many ulcers. The one had moderate destruction of tissue, the other extensive necrosis. The remaining 14 cases showed various degrees of involvement of the colon, most of them having ulcer formation.

It will be noted that in two of the three cases cited the ileum was involved. A third case with lesions in the ileum was in a woman of fifty-six with numerous ulcers and extensive necrosis of the colon. The lower 20 cm. of the ileum was affected in the same way except ulcer formation was not so extensive. This makes three of the 17 cases with lesions of the ileum, a larger proportion than the literature would lead one to believe occurs. Of course such a short series cannot be taken as establishing a percentage of great value.

AMEBIC ABSCESS OF THE LIVER

Three of the cases of amebic dysentery were complicated by abscess of the liver. One was chronic, the others were in the acute stage.

The chronic abscess was in a man of forty. The hepatic flexure of the colon, the duodenum, and the right kidney were adherent to the liver. Through these adhesions the abscess had opened into the duodenum by an opening 2 by 1.5 cm. More than half of the right lobe of the liver was occupied by a cavity containing thick reddish fluid. The wall was fairly smooth, of necrotic liver with a thick layer of new fibrous tissue beneath. In scrapings from the wall were motile amebæ. The lesions in the colon were not extensive. A segment of the lower sigmoid was studded with small ulcers a few millimeters in diameter. The remainder of the colon had only areas of congestion.

One of the acute abscess cases was in a man of 51 years. The conditions present were misleading and the appearance of the lesions in the liver were suggestive of pyogenic rather than amebic origin. The man had gangrenous appendicitis with periappendiceal abscess and peritonitis. In the liver were three cavities, 2 in the right, one in the left lobe, from 2.5 to 4 cm. in diameter and filled with thick yellow fluid, resembling pus. The walls were quite thick

and somewhat rough, the only point against the supposition that the abscesses were metastatic from the appendix. Microscopically the abscesses were typically amebic, including many amebæ. The colon had extensive ulcerative lesions in which were small numbers of amebæ.

The third case of amebic abscess of the liver was in a woman of thirty-three years. She had shortly before been delivered of a dead fetus, had repeated postpartum hemorrhages, and exhibited hemorrhagic endometritis. The liver had fatty infiltration. Throughout the organ, but especially in the right lobe, were numerous cavities from 0.2 to 1.5 cm. in diameter and filled with thick, tenacious, pale yellow fluid. The walls were rough by necrotic tissue. The colon was the site of numerous ulcers in its whole length. Many of these were at the summits of elevated areas the basal portion of which was occupied by thick yellow fluid like that in the liver abscesses. Sections of colon and liver abscesses were those of amebic lesions.

This suppurative appearance of early amebic abscesses of the liver in the second and third cases as opposed to the large abscess in the first with its characteristic chocolate-colored fluid, was very striking. Clinical experience would indicate that when abscesses are large enough to give symptoms and thus become of importance from a diagnostic standpoint, they contain fluid that makes diagnosis practically certain. The different appearance of the small ones therefore would seem to be of pathologic rather than of clinical interest.

Many other findings in these postmortems were of very great interest but their recital would make tedious what has been intended to serve as a brief indication of the material with which we are working. A vast field in investigative tropical medicine is here waiting to be tilled.

A CASE OF SPONTANEOUS, ACUTE AND SUBACUTE PEPTIC ULCERS AND CARCINOMA OF THE THYROID IN A DOG*

By F. C. Mann, M.D., Rochester, Minn.

A SPONTANEOUS gastric or duodenal ulcer is so rare that it may be of value to report finding two gastric ulcers of different degrees of chronicity and an acute duodenal ulcer in a dog with carcinoma of the thyroid. The older gastric ulcer did not show signs of as great chronicity as the peptic ulcer in man, but it more nearly approached such a lesion than any ulcer which I have seen in an animal.

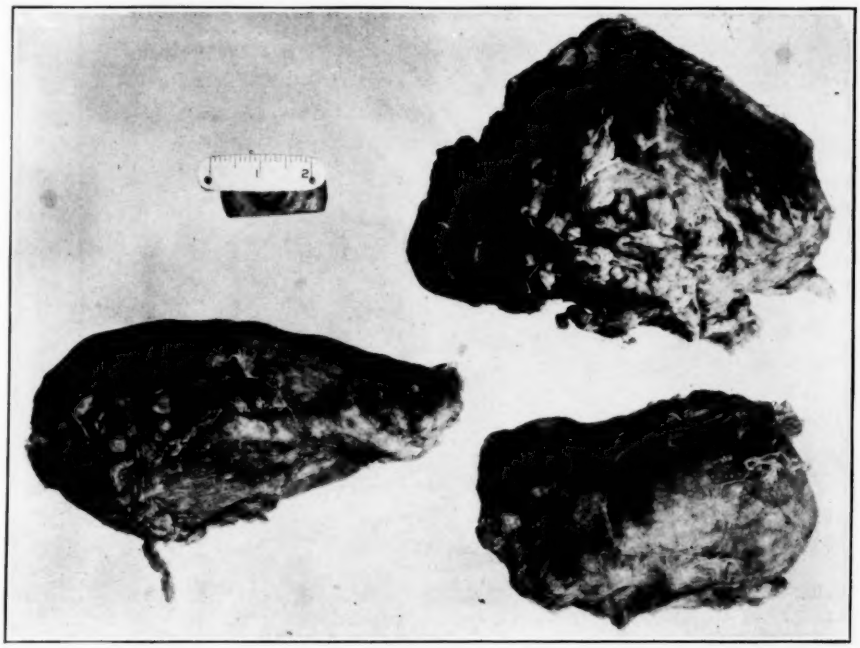

Fig. 1.—Gross specimens of the thyroid and substernal growth. Relative position and size.

DETAILED PROTOCOL

Dog D 519. An old male, Boston bull-terrier, weighing 12.5 kg., was brought to the laboratory Feb. 27, 1920. The animal was very thirsty and drank a large quantity of water which was vomited up almost immediately. At first this excessive drinking was considered responsible for the vomiting. The vomiting continued, however, and the animal ate very little; it died during the morning of February 28.

Necropsy 92 was performed shortly after death. No postmortem changes had occurred. The animal was in good general condition; the omentum was

*From the Division of Experimental Surgery and Pathology. The Mayo Foundation (Graduate School, University of Minnesota).

filled with fat and there was a thin layer of subcutaneous fat. The animal was very old; the teeth were worn down almost to the gums and many were missing. However, no alveolar abscesses were noted. Tonsils could not be found. The thyroid glands were markedly enlarged and nodular. On removal they appeared to show malignant growth throughout. The centers were degenerating and contained many small hemorrhagic areas. The isthmus of the thyroid seemed to be present and projecting from it down into the upper anterior mediastinum was a large growth equal in size to the lobes of the thyroid. Measurements of these lobes were as follows: the right thyroid was 10 cm. by 6 cm.; the left 7 cm. by 4 cm. and the substernal portion was 9 cm. by 5 cm. The three glands ap-

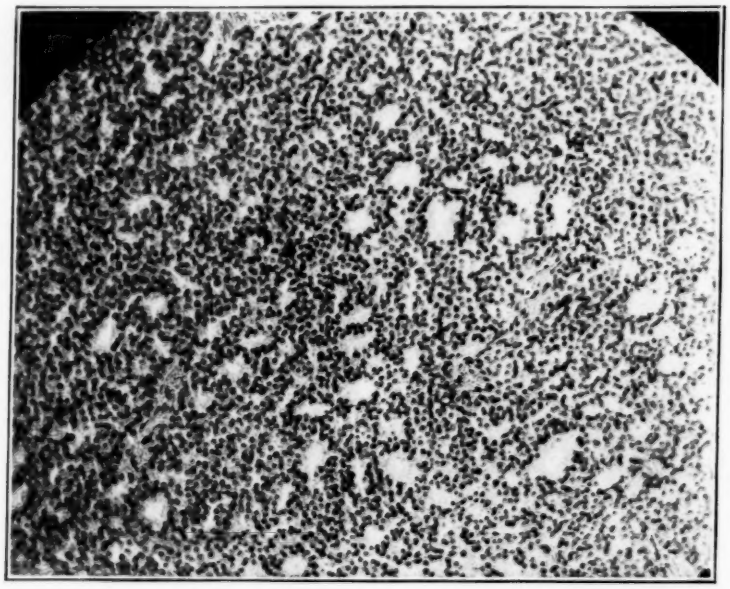

Fig. 2.—Photomicrograph of an area of the substernal growth. Note the thyroid-like arrangement of some of the carcinoma cells. Magnification x100.

peared alike grossly, both intact and on section. They were nodular, the surface quite vascular, and on section they showed large granular nodules interspersed with many large and small hemorrhagic areas (Figs. 1 and 2).

Each lobe of the lung contained from three to eight hard, almost spherical nodules, measuring from 4 mm. to 3 cm. in diameter. On section they were quite homogeneous and faintly granular. They appeared undoubtedly to be metastasis (Figs. 3 and 4).

The abdominal cavity seemed to be free from any infection and at first no pathologic condition could be found except a few small hemorrhagic areas throughout the pancreas.

The kidneys showed a slight amount of nephritis. There were a few small adenomas in the right adrenal. Grossly the spleen, liver, bladder, and prostate appeared to be normal.

When the stomach was opened a large indurated ulcer with raised edges was found 2.5 cm. from the pylorus. This ulcer measured 8 mm. by 15 mm. and

extended through to the muscularis. About 1 cm. from this ulcer, and an equal distance from the pylorus, was another ulcer about 4 mm. in diameter. This ulcer was more acute than the larger ulcer, its walls not being nearly so much indurated. Another ulcer, about 12 mm. in diameter was found just beyond

Fig. 3.—The lung showing a large number of metastatic areas.

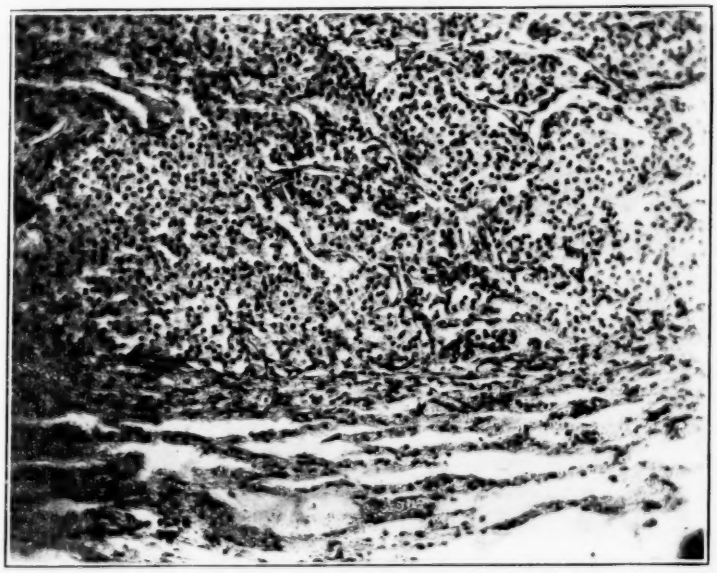

Fig. 4.—Photomicrograph of section of one of the metastatic areas of the lung. Compare with Fig. 3. Magnification x100.

the pyloric ring, in the duodenal mucosa; it had perforated the entire duodenal wall, but was sealed with a thin layer of gastrohepatic omentum; below this was an edge of the pancreas and the edge of a lobe of the liver. The seal was broken while the stomach was being pulled up gently, showing the ulcer perforated into the lesser peritoneal cavity, but no infection was noted (Figs. 5, 6, and 7). The liver showed no evidence of metastasis, and, with the exception of a submaxillary lymph node, no other evidence of malignancy was found elsewhere in the body.

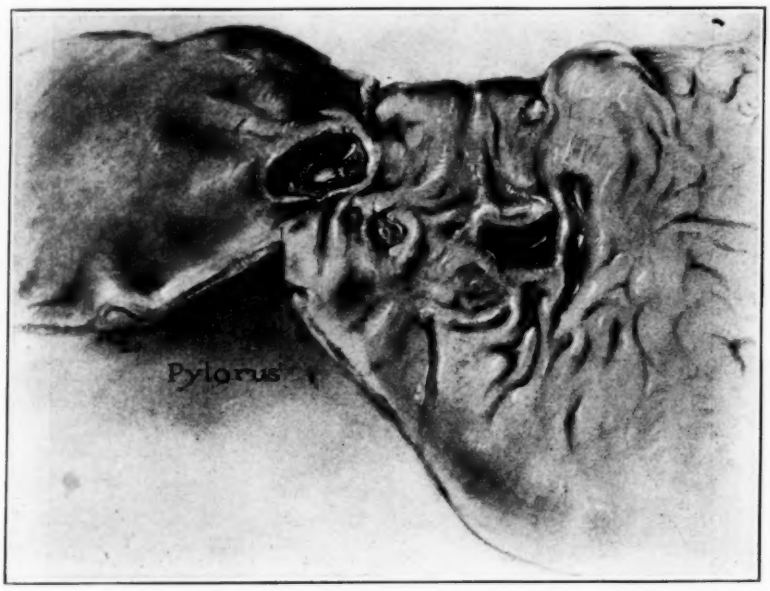

Fig. 5.—Drawing of a location and comparative size of the ulcers. The larger ulcer of the gastric mucosa has a hard indurated base and overhanging edges. The ulcer in the duodenum has completely perforated the duodenal wall.

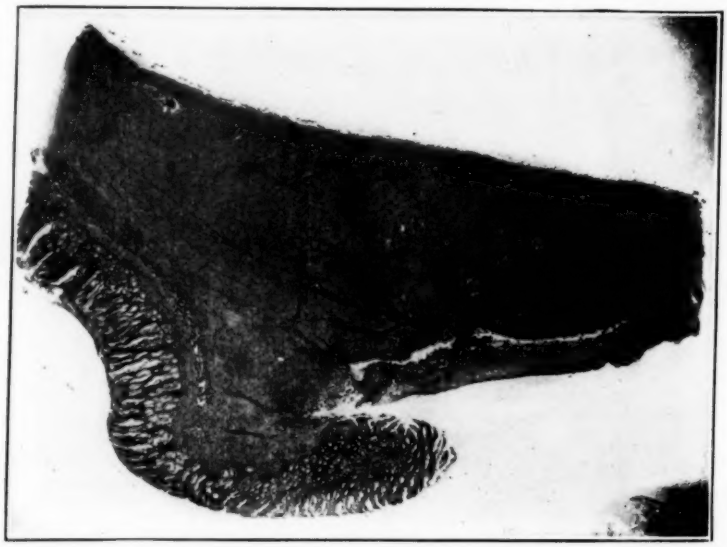

Fig. 6.—Photomicrograph of one edge of the larger gastric ulcer. Note the overhanging edge of the ulcer and the layer of necrotic cell debris at the base. Magnification x9.

MICROSCOPIC EXAMINATION

Microscopic examination of sections of each of the three thyroid specimens showed carcinomatous changes. The metastasis in the lungs also was rather characteristic of a carcinoma of the thyroid. Histologic sections of the ulcers showed the picture characteristic of such conditions. The ulceration in the acute duodenal ulcer was clean-cut, the walls appearing almost as though cut by a knife. There was but slight reaction around the edge of the ulcer which penetrated all coats of the duodenum. The appearance of the larger gastric ulcer was more suggestive of chronicity. It had an overhanging edge of mucosa and the base was covered with necrotic cell debris. Hemorrhagic areas were

Fig. 7.—Photomicrograph of the base of the ulcer shown in Fig. 6. Note the proliferation of young connective tissue. Magnification x100.

found in the muscularis at the base. The connective tissue around the edge and at the base had begun to proliferate and had undoubtedly produced the induration which could be felt on palpation.

The development of the ulcers, it might be reasoned, followed embolic plugging by carcinoma cells of the blood vessels supplying the areas involved. However, there was no evidence of malignant cells in the stomach, and the fact that metastasis could be found nowhere but in the lungs mitigates against such a theory.

LABORATORY METHODS

A SIMPLE METHOD FOR THE REMOVAL OF NATURAL AMBOCEPTOR FROM HUMAN SERA*

By R. L. Kahn, Sc.D., Lansing, Mich.

INTRODUCTION

JUDGING from recent discussions on the removal of natural amboceptor from human sera, it appears that the problem involved is not whether the removal of amboceptor is essential for correct Wassermann tests—this it seems is quite established—but the fact that there apparently exists no simple method for removing amboceptor which meets the requirements of laboratories performing large numbers of tests daily.

The work of Ottenberg,[1] Simon,[2] and others, and more recently that of Kolmer and Rule,[3] definitely proves the importance of removing natural amboceptor from the patients' sera in the Wassermann test. Olmstead's[4] contention that if the tests are read as soon as the controls show complete hemolysis, instead of after keeping them in the ice box overnight, that the presence of natural amboceptor is likely to be insignificant, is in part corroborated by Kolmer and Rule. These investigators report only a very small per cent of false negatives due to natural amboceptor when reading the tests as soon as the controls haemolyze. Granting that the factor of error is not more than one per cent, it is evident that no laboratory can afford to permit this error to enter in its daily work.

The problem involved, however, as was indicated above, appears to be the fact that there is no method for amboceptor removal which is sufficiently practical to render it widely applicable in routine Wassermann laboratories. To quote Von Wedel,[5] "all methods of removing the natural antisheep amboceptor are probably too time-consuming for a routine diagnostic laboratory to perform when large numbers of sera are examined each day." Kolmer and Rule also, in discussing this phase of the question, state that "All methods for the removal of antisheep hemolysin are too time-consuming and laborious for routine absorption of all sera * * * when the examination of fifty or more sera constitutes an ordinary day's work."

The proposed method for the removal of natural amboceptor from the patints' sera, has been applied to 10,000 Wassermann tests and in our opinion meets the requirements of laboratories performing large numbers of tests daily. In this laboratory with about 70 to 130 daily examinations, the element of delay produced by our amboceptor removal method, is practically negligible. Although some theoretical phases of our procedure are still under investigation, we nevertheless feel, in view of the above quotations, that it would be well to present our method at this time.

*From the Bureau of Laboratories, Michigan Department of Health, Lansing, Michigan.

THE METHOD

The method is based on the well-known affinity of sheep-cells for antisheep amboceptor, and consists of adding packed sheep-cells to inactivated serum in the proportion of one drop per c.c. of serum, and permitting the extraction to take place for 10 minutes at room temperature.

In applying this simple procedure, the following factors are to be considered. The packed sheep-cells employed are part of the same cells which, after proper dilution, are used in making the sheep-cell suspension for the Wassermann tests. A quantity of sheep-cells are washed daily with a view of having several extra c.c. of packed cells for the absorption of amboceptor. The drop employed is somewhat smaller than ordinary size, comprising 25 to 30 drops per c.c.

As soon as the serum-tubes are taken out of the inactivating bath, they are lined up in such a manner that variations in quantities of the sera may be easily observable. A drop of packed sheep-cells is then placed in each tube containing approximately one c.c. and shaken gently. To those tubes containing less than one c.c., a part of a drop is permitted to touch the inner side of the tube and the serum brought in contact with the cells by slightly slanting the tube.

Just as soon as cells have been added to all the sera, the tubes are immediately placed in centrifuge holders; balanced, and placed in the centrifuge. By this time, the ten minute extraction period is usually completed; the centrifuge is then started and permitted to run from 6 to 8 minutes. During this centrifugation period, a series of clean tubes are numbered corresponding to those which are in the centrifuge. After centrifugation, the clear supernatant sera are poured into the newly numbered tubes and are ready for use in the Wassermann tests.

DISCUSSION

For an amboceptor removal method to have wide acceptance, it must first be of proved efficacy; second, it must not render the sera anticomplementary and third, it must not be unduly time-consuming.

1. The efficacy of this simple procedure is based on studies carried out in this laboratory on the rate of absorption of amboceptor by packed sheep-cells at various temperatures. A complete report of these studies will be presented in another paper. Suffice it to say in this connection, that it was observed that if an ordinary sized drop of packed sheep-cells is added to 1 c.c. of serum containing 200 units of amboceptor that this small quantity of blood will absorb as many as 160 units of amboceptor in 5 minutes at room temperature. The employment, therefore, of a ten minute absorption period in our procedure, gives a sufficient margin of safety for the absorption of far more amboceptor than is likely to be present in human serum.

We have further tested the dependability of our simple method in the following manner: After fixation of complement by serum and antigen in our regular Wassermann tests, sheep-cells were added (without amboceptor) and incubated in the water-bath at 37° C. for 10 minutes (Kaliski procedure). Natural amboceptor, if present, would thus have had ample time to produce hemolysis of the cells. We have not, however, observed a single instance of

hemolysis—not even in the smallest degree—in 300 such tests carried out at different times, thus proving the efficacy of this procedure.

It might be added that in our opinion, the slight dilution produced by a drop of packed cells in 1 c.c. of serum, does not affect the accuracy of the test. The cells are packed down by centrifugation for 14 minutes at 1600 r. p. m. and if the drop to begin with, is about $\frac{1}{25}$ of a c.c. the amount of saline which remains with the serum, may safely be considered negligible.

2. It is well known that sera acquire anticomplementary properties after prolonged extraction with red cells at incubator temperature, and in order to overcome this property, Rossi[6] suggested a procedure for amboceptor absorption at low temperature. This worker employed chilled centrifuge tubes, chilled corpuscles, and centrifuged in the cold (during warm weather) after keeping the extraction mixture in the ice chest for 30 minutes. The difficulty of applying this method on a comparatively large scale, is very evident.

In our studies on the rate of absorption of amboceptor by sheep-cells, referred to above, we have observed the occasional development of slight anticomplementary properties after a thirty minute, but not after a ten minute extraction period. This anticomplementary phase of our procedure is still under investigation, but there is every indication that a room temperature extraction lasting only 10 minutes, is not sufficient for the development of anticomplementary properties.

3. Regarding the time-consuming element of our procedure, we find that it takes less than five minutes to add 100 drops of sheep-cells to the same number of serum tubes; 10 minutes to balance the tubes for centrifugation; 10 minutes for centrifugation, and 10 minutes to pour the supernatant clear sera in other tubes. These steps are carried out by one worker, while another is looking after the dilution and titration of complement. It is thus evident that the delay produced by this absorption procedure in the completion of the daily tests, is quite insignificant.

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LACTOSE—DETERMINATION OF IN MILK BY COLORIMETRIC METHOD*

By R. G. Owen, M.D., and Roth Gregg, Detroit, Mich.

FOLIN AND McELLROY[1] have described a titration and a colorimetric method for the determination of lactose in cow's and human milk, both of which give quite accurate results. In a later paper, Folin and Peck[2] give more

*From the Chemical Department of the Detroit Clinical Laboratory, Detroit, Mich.

elaborate directions for the preparation of the reagents used in the titration method. Pacini and Russell[3] have likewise described a colorimetric determination of lactose. All these authors make use of picric acid as a protein precipitant.

In their system of blood analysis Folin and Wu[4] have developed the use of tungstic acid as a protein precipitant, and as the use of their reagents and methods have come into quite universal use it occurred to us that the use of these same reagents and technic might simplify the determination of lactose in samples of breast milk.

Our method is simply an adaptation of Folin's[5] latest blood sugar determination to the estimation of lactose. The reagents used are those described by Folin.

METHOD

To 1 c.c. of milk in a 100 c.c. flask add 2 c.c. of 10 per cent sodium tungstate and 2 c.c. of ⅔ normal sulphuric acid, the latter drop by drop. Mix and let stand 5 minutes. Dilute to 100 c.c. and filter. We find that 2 c.c. each of tungstate and acid give clearer filtrates than where only 1 c.c. of each is used.

Place in a Folin special sugar tube 1 c.c. of filtrate and 1 c.c. of water, to balance volume in tube, add 2 c.c. respectively of standards A & B to two other sugar tubes. To the unknown and the standards add 2 c.c. of alkaline copper solution and place in boiling water 6 minutes. Place tubes in cold water until cooled, then add 2 c.c. of Folin molybdate phosphate solution and let stand a few minutes.

Dilute the three solutions to 25 c.c., mix and read in the colorimeter, using that standard which most nearly matches the unknown and setting the standard at 20.

Standards. Make up an accurate 1 per cent lactose solution in distilled water using purified lactose. We have obtained our lactose from the Digestive Ferments Co., Detroit, Mich. Add a little toluol. We have found that this stock solution keeps well for several months. Standard 1, of which 2 c.c. contains 0.5 mg. lactose is made by diluting 12.5 c.c. of the 1 per cent stock lactose solution to 500 c.c. Standard 2, containing 0.7 mg. per 2 c.c. is made by diluting 17.5 c.c. of the 1 per cent solution to 500 c.c. Preserve these solutions with toluol and make up fresh about once a month.

$\frac{\textit{Standard Reading}}{\textit{Unknown Reading}}$ x 5, if standard 1 is used, or times 7 unknown reading if Standard 2 is the one selected will give the grams of lactose per 100 c.c. of milk.

Figures obtained by the above method of estimating lactose check very well with the Folin titration method. Moreover, lactose added to various samples of milk can be quantitatively recovered to within a few milligrams.

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A SIMPLE SHAKING DEVICE

By J. P. Baumberger, Stanford University, California

RECENTLY we had occasion to make an impromptu shaking device which has proved very satisfactory. The apparatus makes use of a discarded foot-driven machine similar in structure to a sewing machine. As much foot-driven apparatus is available in laboratories, or can be readily obtained for a song, we believe the following description will not be amiss:

An old color-mixing bench formed the principal part of the apparatus. The driving rod (*E*, Fig. 1), of the bench, extending from the foot-pedal to the crank-shaft (*D*) was disconnected from the pedal and fastened with strap iron (*F*) to the middle of the upper edges of the end and partitions of a box (*G*).

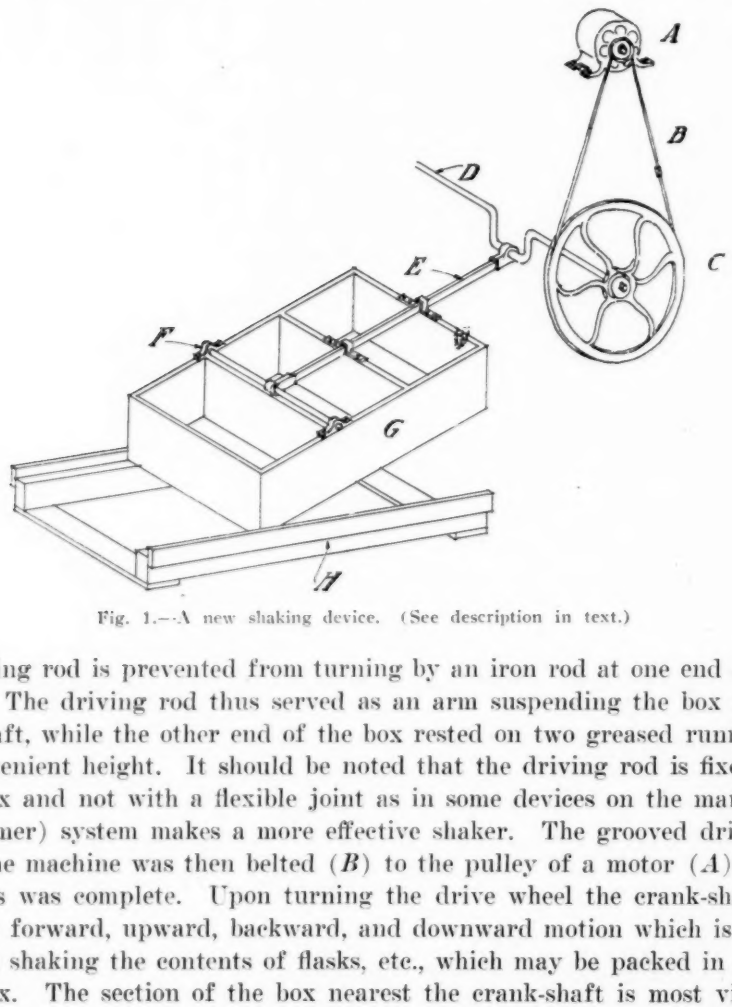

Fig. 1.—A new shaking device. (See description in text.)

The driving rod is prevented from turning by an iron rod at one end as shown at (*F*). The driving rod thus served as an arm suspending the box from the crank shaft, while the other end of the box rested on two greased runners (*H*) at a convenient height. It should be noted that the driving rod is fixed firmly to the box and not with a flexible joint as in some devices on the market, and this (former) system makes a more effective shaker. The grooved drive wheel (*C*) of the machine was then belted (*B*) to the pulley of a motor (*A*) and the apparatus was complete. Upon turning the drive wheel the crank-shaft gives the box a forward, upward, backward, and downward motion which is very effective in shaking the contents of flasks, etc., which may be packed in excelsior in the box. The section of the box nearest the crank-shaft is most vigorously shaken and the third section only gently agitated.

DETERMINATION OF COAGULABLE PROTEIN IN SERUM*

By W. N. Berg, Ph.D., Washington, D. C.

THEORETICALLY, the determination of total coagulable protein in serum or a similar material is simple. It is only necessary to dilute the serum with about 20 volumes of water, add dilute acid to neutrality, heat to the boiling point and the coagulable protein is precipitated in large flocculi which makes subsequent filtration easy. The precipitate is weighed after drying to "constant" weight. In actual practice the numerous sources of error lead to the use of indirect methods; for example, the protein content of a serum is determined, by the use of the refractometer; the nephelometer, etc. For a discussion of these methods see Robertson.[1] The method of filtering the coagulated protein on to weighed filter papers, and weighing the dried precipitate plus the paper in weighing bottles, as described by Berg[2] is open to two objections as previously pointed out: (1) the difficulty of drying filter paper and coagulated protein to constant weight in such fashion that while water is being driven off, oxidation shall not take place; (2) the method requires comparatively large quantities of serum, i.e., 5 or 10 c.c. This is more than is available in many immunologic studies.

A method was desired that conformed to the following requirements: (1) it must be direct, so far as the coagulable protein is actually coagulated, dried and weighed; (2) a single determination must be possible in a small quantity of serum, i.e., 0.50 c.c.; (3) the coagulable protein obtained and weighed must represent the actual total coagulable protein in the original sample with a high degree of accuracy. The method herein described meets these requirements. Considering the results obtained, its advantages over other methods justifies its use.

PIPETS

One c.c. pipets graduated into 0.01 c.c., were used for measuring the 0.50 c.c. portions of serum used in a single determination. The length of these pipets between the 0 and 1.00 c.c. marks was approximately 250 mm., so that reading the pipet to a small fraction of 0.01 c.c., was not difficult. These pipets were specially made; because the usually graduated pipets have the 0.01 c.c. divisions too close together. An error in measurement of 0.01 c.c. of serum is unnecessary with properly made pipets. All were standardized by the Bureau of Standards.

The question naturally arises whether a pipet of the Mohr type, which will deliver 1.00 c.c. of water will deliver 1.00 c.c. of serum which is much more viscous than water. The following results were obtained from three concordant weighings of water and serum delivered by a 1.00 and 5.00 c.c. pipet; the sample of Berkefeld filtered normal horse serum had a specific gravity of 1.0354

*From the Pathological Division, Bureau of Animal Industry, United States Department of Agriculture.

at 30° C., and contained 0.0752 grams solids-not-ash in 1.00 c.c. One c.c. pipet No. 19814 delivers 0.994 c.c. water at 20° C., according to Bureau of Standards certificate. This pipet delivered 0.990 c.c. water or 0.979 c.c. serum at 32° C. Similarly, 5 c.c. pipet No. 19820, certified to deliver 5.010 c.c. water at 20° C., delivered 4.985 c.c. serum at 30° C. The observed difference between the volume of water and serum delivered in the 1.00 c.c. pipet, i.e., 0.994-0.979 or 0.015 c.c., was for unrestricted outflow; because the pipets are calibrated that way. But in actual measurement of serum for analysis, the outflow is restricted somewhat, so that delivery is slow; this makes for accurate reading of the pipet and diminishes the error due to viscosity. For all practical purposes the volume of serum delivered for a single determination, *i.e.*, 0.50 c.c., differs from 0.50 c.c. by a negligible amount. The weighings were made in glass-stoppered, weighing bottles and corrections were made for loss by evaporation: this amounted to from 2 mgs. in 30 seconds to 6 mgs. in 3 minutes.

CENTRIFUGE TUBES

These were heavy-glass, bacteriologic test tubes without lip; outer dimensions, length 95 mm., diameter, 17 mm., average weight 11.5 grams; maximum capacity 13-15 c.c.; numbered consecutively with hydrofluoric acid. Before use these were cleaned in hot sulphuric-acid, potassium-bichromatic mixture, rinsed in distilled water, dried at 100° C. and kept in a dessicator till needed. The same tubes can be used repeatedly; between determinations their weights did not vary more than 0.1 or 0.2 mg. Some of the tubes lost no weight after ten treatments with acid-bichromate mixture. Such tubes are much more constant in weight than dry filter papers; they are quickly weighed to a 0.1 mg. and are not hygroscopic. As an example, Tube No. 10, weighed originally 12.4946 grams, did not weigh less than 12.4944 or more than 12.4948 grams during the course of 11 weighings and 10 treatments with acid bichromate mixture in three years. None showed greater variation. Twenty-four is a convenient number to have on hand.

CENTRIFUGE

This was a medium-sized, motor-driven centrifuge, head approximately 180 mm. in diameter, carrying 8 tubes. It was run at 2400 revolutions per minute for 20 to 25 minutes during a determination.

COAGULATING THE PROTEIN

The samples of serum, taken from the refrigerator are allowed to come to room temperature. Determinations should be made in triplicate. Into each of three clean, weighed tubes, pipet 0.50 c.c., of the sample. Obviously the greatest care should be used to avoid error in measurement. From a buret measure 9 c.c. distilled water into each tube.

The object of the following procedure is to gradually neutralize the alkalinity of the serum with dilute acetic acid, aided by heat, and to coagulate the protein by bringing to a boil after neutralization is effected. In this way hydrolysis of protein by acid or alkali is avoided.

From 0.7 to 1.0 c.c. n/50 acetic acid are usually required for maximal precipitation of protein in 0.50 c.c. serum. Heat the tube over a small Bunsen flame until the tube is hot to the hand, but the contents do not approach a boil. Add the n/50 acetic acid, at first trying 0.2-0.3 c.c. A precipitate should form which will dissolve on rotating the tube, giving the contents an opalescent appearance. Add 0.2-0.3 c.c. more acid; each addition of acid precipitates protein which will redissolve when the tube is rotated, so long as the amount of acid added is insufficient for complete precipitation. Heat the tube after each addition of acid, but do not approach a boil. As the amount of added acid is increased, the contents become more and more milky, until presently the protein flocculates. This can be easily observed. Add no more acid; heat the tube almost to a boil, let stand a few minutes. Time required for flocculating one tube is about 5 minutes.

SOME TYPICAL ANALYSES

DESCRIPTION OF PRODUCT	USED IN EXP. NO.	DATE OF DETERMINATION OF COAGULABLE PROTEIN	MILLIGRAMS OF COAGULABLE PROTEIN ACTUALLY WEIGHED FROM 0.50 C.C.	C.C. N/50 ACETIC ACID USED
Tetanus antitoxin 420 F	20	Aug. 8, 1917	31.2	0.1
			31.9	0.1
			32.1	0.1
	21	Oct. 12, 1917	32.5	0.1
			32.6	0.1
	3	Apr. 1, 1920	28.4	0.45
			31.9	0.55
	3	May 6, 1920	28.8	0.15
			30.0	0.15
			31.1	0.10
Tetanus plasma 9588	4	Apr. 20, 1920	28.4	1.1
			29.8	1.0
			36.5	1.1
	4	Apr. 23, 1920	33.0	1.2
			41.0	1.2
			42.9	1.2
	4	June 9, 1920	44.2	1.3
			44.8	1.3
			45.4	1.3
Tetanus serum 2030	5	May 28, 1920	39.7	0.8
			39.8	0.9
			40.1	0.8
	5	June 12, 1920	39.2	0.7
			40.5	0.8
			40.6	0.8
Diphtheria serum 2401	9	June 29, 1920	33.1	0.7
			33.2	0.7
			33.1	0.8
			35.1	0.8
			35.7	0.8
			35.3	0.9
			35.9	0.9
			36.0	0.9

When precipitation is maximal the supernatant fluid is water clear. If there is any cloudiness or opalescence, this is an indication that maximum precipitation has not been obtained. In such a case add 0.1 to 0.2 c.c. n/50 acetic acid, and heat for a minute. Sometimes this improves the result. Rotating the

tube so that the large flocculi mix with the fluid seems to improve matters by enabling the larger flocculi to pick up mechanically very small particles of coagulum. Obviously, the second and third tubes will generally give better results.

The tubes are centrifuged for 20 minutes at 2400 revolutions per minute. The coagulated protein packs firmly to the bottom of the tube. After centrifuging, the supernatant fluid is poured off: the tubes may be inverted without loss of coagulum. The reaction of the supernatant fluid in several determinations was found to be $P_H = 6.6$, showing that the precipitation took place in the presence of but traces of acid. Allow the tubes to drain well. The outsides of the tubes are cleaned by immersing them to about ¾ of their height in strong sulphuric-acid, bichromate mixture, rinsing and drying with a towel.

The tubes are transferred to a vacuum desiccator and dried for 48 hours at room temperature; weighed, dried for a second 48 hours and again weighed to 0.1 milligram. The drying period may, however, be shortened. When the desiccator contains fresh acid, drying overnight generally gives a result that for practical purposes is correct. Further drying generally results in the loss of a fraction of a milligram. In every case constancy of weight was ascertained by at least two weighings.

The weights of coagulable protein in the subjoined table, typical of many others are the differences between the weights of the tubes and the tubes plus precipitate dried. When cleaned in bichromate mixture, washed, dried and weighed, the tubes are ready for the next determination.

Precipitates obtained from tubes containing a cloudy or milky supernatant fluid are invariably low and must be rejected. As the figures in the subjoined table show, the technic, properly used, will give results on the same sample that differ from one another by only a fraction of a milligram.

SOLIDS-NOT-ASH

It was considered desirable to ascertain what part of the total solids-not-ash in serum was precipitated by acetic acid in the determinations of coagulable protein. The solids-not-ash was determined as follows:

Duplicate portions of 1.00 c.c. of the serum were pipetted into small porcelain crucibles. These were transferred to a vacuum desiccator and dried at room temperature to constant weight. This gave the weight of total solids. The crucibles were then transferred to an electrically heated, muffle furnace and the contents ignited at a low red heat. Weight of total solids minus weight of ash gave solids-not-ash. These determinations can be carried out very accurately and involve no difficulty.

In nine series of determinations, on the products mentioned in the Table, the coagulable protein precipitated by acetic acid amounted to an average of 91.4 per cent of the solids-not-ash; the extremes were 89.2 and 94.2 per cent.

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EDITORIALS

Blood Sugar Tolerance in Cancer and in Hypertension

THERE is no doubt that there are serious difficulties in diagnosis of gastro-intestinal carcinoma, and that this is especially true of diagnosis in the early stages of malignancy. So, say Friedenwald and Grove, in spite of our modern methods of investigation, the diagnosis in many instances remains obscure often until late in the progress of the disease and is frequently not revealed until exploratory incision establishes the true nature of the affection. Any additional help therefore which may lead to the solution of this difficult problem cannot but be of the greatest value. In the blood sugar tolerance test these authors believe there has been added a procedure of real value.

The test is carried out in the following manner: After a night's fast 100 grams of dextrose dissolved in 300 c.c. of black coffee is given the patient. Just before this is given, blood is taken for a sugar test, and this procedure is repeated 45 minutes and 120 minutes after the ingestion of the sugar. The urine may be tested for sugar 120-180 minutes after the glucose meal, but is not essential.

The writers point out that Freund, in 1885, showed that there is always a hyperglycemia in carcinoma cases, and that there is none in sarcoma cases.

Later, Trinkler concluded that hyperglycemia is always present in carcinoma cases, and that in carcinoma of the internal organs this was of greater degree than in carcinoma of the skin or mucous membrane. He also pointed out that there was no relation between the hyperglycemia and cachexia. Rohdenburg, Bernhard and Krehbiel were the first to make careful investigations on sugar tolerance in cancer, and they showed that while a normal individual gives an increase in the blood sugar which reaches its maximum in 45 minutes and which then gradually falls to normal, the cancerous person, beginning with a normal blood sugar, shows a rise in 45 minutes, after which time it may continue to rise or remain stationary for 120 minutes after the glucose meal. At the end of this time the blood sugar begins gradually to recede and becomes normal not earlier than in 180 to 240 minutes after the feeding. Benedict and Lewis in a series of 53 patients showing malignancy, took the blood 180 minutes after ingestion of food. Of these 36 per cent showed a marked increase in blood sugar. At least 49 per cent showed a tendency to hyperglycemia. Benedict and Lewis point out that there is a steady increase in blood sugar as the disease progresses, and a maximum is reached just prior to death.

In the recent study of Rohdenburg, Bernhard and Krehbiel, based upon 228 cases, the authors call attention to three types of reaction following the sugar tolerance test. In the first the blood sugar at the 45 minute interval rises above the zero hour figure and at the 120 minute interval is as high or higher than at the 45 minute interval. In the second type the 45 minute reaction is similar to that of the first type, but at the 120 minute interval the figure is almost that of the zero hour. In the third type the initial blood sugar concentration is higher than, or the same as, that at 45 minutes, and at 120 minutes is the same or higher than the original figure. Nephritis in 75 per cent of the cases gave a type 2 reaction; tuberculosis in 60 per cent, gave a type 1; syphilis in 72 per cent, gave type 2; diabetes in 60 per cent gave a type 2; pregnancy in 66 per cent gave a type 1; 61 per cent of gastric carcinomas and 50 per cent of intestinal carcinomas gave a type 1 reaction.

Friedenwald and Grove studied 32 typical cases of carcinoma of the gastrointestinal tract. In addition they observed 3 cases of uterine carcinoma, 1 case of mammary cancer, 1 case of carcinoma of the prostate and spine, 1 case of uterine fibroid, 2 cases of sarcoma, 8 cases of peptic ulcer, 2 cases of gastric syphilis, 3 cases of diarrhea and dysentery, 8 cases of achylia gastrica and chronic gastritis, 4 cases of cholelithiasis, 2 cases of chronic appendicitis, 11 cases of enteroptosis, 5 cases of nervous dyspepsia, and 5 cases of intestinal stasis and mucous colitis. In addition they studied 4 perfectly healthy persons.

Their conclusions are that there is usually present in carcinoma of the gastrointestinal tract a rather characteristic curve of sugar tolerance which differs somewhat from that observed in carcinoma of other regions of the body. This curve presents a high sugar content, even in the fasting state, followed by an initial rise up to 0.24 per cent, or even higher within 45 minutes after the ingestion of the dextrose, remaining at this level for at least 120 minutes and at no time falling below 0.20 per cent. This test the authors say is rather distinctive and is of value in distinguishing between carcinoma and the other diseases of the digestive tract. As an aid in early diagnosis they are not definite,

but they say that since the reaction is characteristic regardless of the extent of the involvement it is to be presumed that it is present in early cases. They realize that the test is not specific of carcinoma and that it cannot be relied upon alone, in other words it is not pathognomonic. Nevertheless it appears that in cases of gastrointestinal disease in which there is some evidence of carcinoma, i.e., in differential diagnosis, the test may have a very important bearing, especially if diabetes, nephritis, tuberculosis, and thyroid disturbances have been excluded.

It has already been mentioned in the foregoing paragraphs that nephritis is one of the conditions in which glucose metabolism is upset, that nephritic patients react abnormally to the glucose tolerance test. With diabetes the same is true. Patients with chronic vascular hypertension may also show a disturbance in handling glucose. This type of case is very similar to the nephritic with hypertension. It is with a group of chronic vascular hypertension cases that O'Hare has concerned himself. He says that while following a large group of these cases it was noted that from time to time some of them showed a trace of sugar in the urine, occasionally enough to quantitate. The suggestions were made that these were cases of renal diabetes, or that they were incipient true diabetes. To test these suggestions the glucose tolerance test of Janney and Isaacs was used, *i.e.*, the fasting blood sugar is determined and then 1.5 grams of glucose per kilogram of body weight, with 2.5 grams of water per gram of glucose was given. The blood sugar was determined 2 hours later, and the urinary sugar, 3 hours after the glucose meal.

The results of the application of this method are interesting indeed, as they appear in the chart in the original article, for, while certain cases by themselves give no striking results, when all are arranged in the order of the degree of the reaction, they form a scale which runs from normal to a point approaching the typical diabetic reaction. This suggests to O'Hare that these cases are potential diabetics.

—*P. G. W.*

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Present Day Immunology

THE authoritative statement of present day immunology has been made; Jules Bordet has written a "Treatise on Immunity in the Infectious Diseases."[1] It will perhaps come as a surprise to those who have not followed attentively the investigations of the Belgian scientist to find that although great as a discoverer he is equally great as an expositor. Bordet is a master of that flexible and exact tongue that has no equal for scientific exposition and instruction. The French have a knack of repetition of the essential facts from multiple points of view with ingenius turns of phrasing that rejoices the ac-

[1]Bordet: Traité de l' Immunité dans les maladies infectieuses, Masson & Co., Paris, 1920.

customed eye or ear, and produces an indelible impression that is never equalled by the boiled down essence of protocols.

And the scientific use of the imagination that has made Bordet so fertile in experimentation is evident here also. The book is not simply an evaluation of acquired facts, but full as well of ingenious working hypotheses. The very success of this investigator lies in the fact that he has always approached new facts untrammeled by preconceived notions. And yet Bordet's explanation of his and others results, although strikingly free from convention, seems in last analysis the simplest explanation, the freest from unjustifiable assumption.

Bordet's book is an extensive one comprising over 700 pages and divided into four main sections dealing respectively with a general survey of the field; with cellular immunity; with humoral immunity; and with the reaction of the organism in its entirety. So far the treatise is orthodox enough. The well established and understood facts are fully and ably discussed. It is in the treatment of the ill-defined and undeveloped fields that the ingenuity of the author has full play and raises a series of ingenious questions and offers numerous suggestive hypotheses. It was some fifteen years ago that Bordet expressed to the reviewer the desire for a few months freedom from routine to indulge in an assembling and calm contemplation of the facts that had been demonstrated in his particular field. He felt the assurance that out of such a survey would come new leads of promise. The isolation came, not in the way he had imagined and for a longer period, and although the contemplation under German duress could scarcely be regarded as calm, the survey and recapitulation have been made. We may look forward eagerly to the new lines of investigation that his study will stimulate in himself and his pupils.

Particularly original is the treatment of such questions as: anaphylaxis; the nature of specificity; partial immunity; the relations of phagocytes to parenteral digestion; auto cytotoxins in their relation to chronic disease; and many others. It is to be hoped that a translation will soon render this valuable and authoritative work more readily accessible to the English speaking world.

—F. P. G.

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*Epidemiology of Tuberculosis**

COLONEL BUSHNELL, who so long and so successfully conducted the army tuberculosis hospital at Fort Bayard, N. M., and who had charge of the tuberculosis division in the Surgeon General's Office during the War, has given us a most valuable and readable book on tuberculosis. He has collected a great deal of information along lines which hitherto has not received adequate attention. Bushnell divides the peoples of the world into tuberculized and nontuberculized races. In the former, tuberculosis is a chronic, slowly progressive, relatively benign disease. In nontuberculized races, it is an acute, epidemic, highly fatal disease. Certain localities, especially in tropical and semitropical countries, have had the reputation of being free from tuberculosis, but when an attempt has been made to use these places as resorts for those afflicted with this disease the natives have quickly developed the disease and supplied a very high death rate. In our own country we have in large numbers, so far as races are concerned, the white, the negro, and the Indian. Bushnell shows, especially by statistics of deaths in Charleston, S. C., that before the Civil War the tuberculosis death rate among whites and blacks was about the same. He concludes from this that even then the negro race was already tuberculized. Immediately following the Civil War the death rate among negroes rapidly increased and soon exceeded, and has continued to exceed, the death rate from this disease among the whites. The great increase in the death rate from tuberculosis among the blacks after the Civil War is attributed by Bushnell to poverty and bad housing conditions. He says: "The facts adduced as to the tuberculosis of the negro justify the following conclusions: the negroes as a race in the United States have long been in contact with the virus of tuberculosis. They are probably as well or nearly as well tuberculized as the white race. This is shown by the fact that when they were slaves, when their masters gave regular employment, provided food and to some extent looked after their health, their tuberculosis rates differed little from those of the whites. When their emancipation thrust them unprepared into the struggle for existence their sufferings and errors are revealed in an enormously increased mortality not only from tuberculosis but from other diseases."

Bushnell is quite certain that tuberculized races acquire a certain degree of immunity to the disease. This immunity is in no sense inherited, but must be acquired by each individual, and the danger lies in the acquisition of this im-

*A Study in the Epidemiology of Tuberculosis with Especial Reference to Tuberculosis of the Tropics and of the Negro Race by George E. Bushnell, Ph.D., M.D., William Wood & Co., New York, 1920.

munity. He says: "Civilized man can never escape the dangers of infection with the tubercle bacillus. But if we did escape the dangers of infection, we should also lose the benefits of tuberculization. Supposing that with extraordinary energy and sagacity we banish all tuberculosis from our town and rear an absolutely uninfected group of children. Having passed childhood under the irksome restrictions that would be necessary, the time must come when they shall be permitted to enter the outside world, for the fear of disease cannot remain the paramount consideration during life. As soon as, now adults or adolescents, they leave the sheltering confines of their native town, they will be exposed to the dangers of primary tuberculous infection and that at an age when the world beckons most invitingly and when prudence is least developed. In fact they would be in a hardly less dangerous situation than the tropical native when he first enters a civilized community. Prophylaxis has simply resulted in exchanging the danger of a chronic and usually relatively benign infection for the danger of an acutely fatal infection."

Bushnell is of the opinion that our Indians are just now becoming tuberculized and that in consequence of this the birth rate is now exceeding the death rate and the Indian promises to not disappear from the earth but to multiply and reproduce his kind. In 1891 an effort was made to try the Indian as a soldier. Authorization was obtained for eight troops of Indian Cavalry and nineteen companies of Indian Infantry. In the years immediately following, over eight hundred Indians were enlisted in the army and made up exclusively Indian organizations, but on account of the wide and deadly prevalence of tuberculosis among them this plan was given up.

It has been proposed that all children sent to the Indian schools should be tested with the tuberculin test and that those giving response to this test should not be sent to the schools. Bushnell comes to an opposite opinion and says: "In the writer's judgment, children should not be allowed to attend the larger schools unless they have a positive skin reaction to tuberculin. There is danger here that those who react positively may be on the point of breaking down with manifest tuberculosis of severe type, so that long railway journeys will lead to disaster. We would therefore make the further suggestion that no Indian child be sent to boarding school unless he is in apparently good health, shows at least no marked glandular involvement, gives no physical signs of tuberculosis of the lungs and has been positive for the Pirquet reaction for at least one year. In other words, a tuberculous vaccination should be required as well as a vaccination against smallpox."

Bushnell is of the opinion that we should give special attention to the protection of our children, and this attention should consist in endeavoring to prevent massive infection among them. There is only one logical conclusion to Bushnell's views and he does not hesitate to draw it—we must find some method of vaccination against this disease. We quite agree with the author that the greatest hope in the eradication of tuberculosis lies in the possibility of successful vaccination.

—*V. C. V.*